Factors Predictive of Severe Hypoglycemia in Type 1 Diabetes

Analysis from the Juvenile Diabetes Research Foundation continuous glucose monitoring randomized control trial dataset

JUVENILE DIABETES RESEARCH FOUNDATION CONTINUOUS GLUCOSE MONITORING STUDY GROUP*

OBJECTIVE—Identify factors predictive of severe hypoglycemia (SH) and assess the clinical utility of continuous glucose monitoring (CGM) to warn of impending SH.

RESEARCH DESIGN AND METHODS—In a multicenter randomized clinical trial, 436 children and adults with type 1 diabetes were randomized to a treatment group that used CGM (N = 224), or a control group that used standard home blood glucose monitoring (N = 212) and completed 12 months of follow-up. After 6 months, the original control group initiated CGM while the treatment group continued use of CGM for 6 months. Baseline risk factors for SH were evaluated over 12 months of follow-up using proportional hazards regression. CGM-derived indices of hypoglycemia were used to predict episodes of SH over a 24-h time horizon.

RESULTS—The SH rate was 17.9 per 100 person-years, and a higher rate was associated with the occurrence of SH in the prior 6 months and female sex. SH frequency increased eightfold when 30% of CGM values were ≤70 mg/dL on the prior day (4.5 vs. 0.5%; $P < 0.001$), but the positive predictive value (PPV) was low (<5%). Results were similar for hypoglycemic area under the curve and the low blood glucose index calculated by CGM.

CONCLUSIONS—SH in the 6 months prior to the study was the strongest predictor of SH during the study. CGM-measured hypoglycemia over a 24-h span is highly associated with SH the following day ($P < 0.001$), but the PPV is low.

Diabetes Care 34:586–590, 2011

Current constraints in blood glucose monitoring and insulin delivery technologies limit the ability of most individuals with type 1 diabetes to safely achieve and maintain recommended glucose and hemoglobin A_{1c} (HbA_{1c}) targets. Severe hypoglycemia (SH) remains a common side effect of intensive treatment and a major barrier to achieving normoglycemia in type 1 diabetes. Several prior studies have evaluated factors associated with an increased risk of SH. In a study of 1,190 children and adolescents with type 1 diabetes, Craig et al. (1) reported that younger age, male sex, longer duration of diabetes, and intensive insulin therapy (≥3 injections/day) were associated with an increased risk of SH. In a study of 60 individuals, mainly adults, with insulin-dependent diabetes, Gold et al. (2) reported that the occurrence of SH was associated with prior SH, hypoglycemia unawareness, older age, and autonomic dysfunction. In the Diabetes Control and Complications Trial (DCCT) (3), an analysis of the first 424 intensively treated subjects found that predictors of SH in the intensive group included prior SH, longer duration of diabetes, higher baseline HbA_{1c}, lower recent HbA_{1c}, and higher baseline insulin doses. A later analysis of all 1,441 subjects found that a higher SH rate in both treatment groups occurred in subjects with prior SH, longer duration of diabetes, absent residual C-peptide secretion, younger age (adolescents compared with adults), and higher baseline insulin doses; the rate was higher in females than males in the conventional group but not in the intensive group and higher in those with lower baseline HbA_{1c} in the conventional group but not the intensive group (4).

Recurrent episodes of mild hypoglycemia appear to cause defects in counterregulatory hormone responses to subsequent hypoglycemia placing patients with type 1 diabetes at increased risk of severe hypoglycemia. This sequence of events has been termed hypoglycemia-associated autonomic failure. The evidence supporting the development of hypoglycemia-associated autonomic failure was initially demonstrated in clinical research center–based hypoglycemic clamp studies, and a relationship between the risk of SH and antecedent biochemical hypoglycemia in the free living condition also has been reported (5).

The Juvenile Diabetes Research Foundation (JDRF) Continuous Glucose Monitoring Study Group recently reported the results of a 6-month randomized clinical trial and a 6-month extension study that evaluated the effectiveness of real-time continuous glucose monitoring (CGM) in 451 intensively treated type 1 diabetes subjects who had baseline HbA_{1c} levels both within and above the target range (6–11). These studies provided a large dataset to evaluate the association of clinical and demographic factors with the development of SH. In addition, longitudinal CGM glucose data were available to evaluate the relationship between biochemical hypoglycemia detected by CGM and subsequent SH.

RESEARCH DESIGN AND METHODS

METHODS—The study protocol and clinical characteristics of enrolled subjects have been described in detail (7–9). Major eligibility criteria included age ≥8 years, type 1 diabetes for at least 1 year, use of

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Received 11 June 2010 and accepted 29 November 2010.
DOI: 10.2337/dc10-1111. Clinical trial reg. no. NCT00406133, clinicaltrials.gov.
This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc10-1111/-/DC1.
*Members of the writing committee are listed in APPENDIX, and a full group listing is available in the Supplementary Data online.

either an insulin pump or multiple (at least three) daily insulin injections, and HbA_{1c} level <10.0%. Prior SH was not an exclusion and 8% of subjects in both treatment groups self-reported at least one SH event in the 6 months prior to study entry. The study consisted of a 6-month randomized trial in which subjects were randomized to either a control group that used standard home blood glucose monitoring or a CGM group that used one of the following three CGM devices: the FreeStyle Navigator (Abbott Diabetes Care, Inc., Alameda, CA), the MiniMed Paradigm REAL-Time Insulin Pump and Continuous Glucose Monitoring System (Medtronic MiniMed, Inc., Northridge, CA), or the DexCom SEVEN (DexCom, Inc., San Diego, CA). The randomized trial was followed by a 6-month extension study in which CGM was initiated in the control group and continued in the CGM group.

Analysis was limited to 436 (97%) of 451 randomized subjects who completed 12 months of follow-up. The 15 subjects with incomplete follow-up included one subject who was believed to be factitiously producing SH by intentional insulin overdose and 14 others who did not experience SH before dropping out of the study.

SH was defined as an event that required assistance from another person to administer carbohydrate, glucagon, or other resuscitative actions (3). The proportional hazards model was used to evaluate the association of baseline demographic and clinical factors with the occurrence of SH events in univariate models. Factors in the univariate models with a P value < 0.20 were included in an initial multivariate model and then a backward elimination procedure was used to remove variables with a P value > 0.05. However, because of multiple statistical comparisons, only P values < 0.01 were considered significant.

A forward selection process resulted in a similar model. To avoid colinearity in the model building, only one baseline CGM measure of hypoglycemia (percentage of values ≤70 mg/dL) was included in the models. Results were similar for the highly correlated hypoglycemic area under the curve (AUC) and the low blood glucose index (LBGI) (12) calculated from CGM data (data not shown). CGM measures of glycemic variation such as SD, coefficient of variation (defined as SD divided by the mean glucose), and the absolute rate of change (13) were also confounded with percentage of CGM values ≤70 mg/dL and were excluded from the models. Subjects with missing values for covariates were excluded from the corresponding univariate models. For the multivariate models, missing values were treated as a separate category for discrete covariates, and an indicator for missing values was added to the model for continuous covariates.

The SH rates in the control group and CGM group during their first 6 months of usage were compared using a Wilcoxon rank sum test. A paired signed rank test was used to compare the SH rate of the CGM group between the first and second 6 months. A repeated-measures logistic regression with generalized estimating equations was used to compare the SH rate between days with and without CGM use.

A second analysis evaluated the association of four CGM hypoglycemia indices (% ≤70 mg/dL, hypoglycemic AUC, LBGI, and at least 30 consecutive min ≤54 mg/dL) during 1 day with the occurrence of SH on the following day using repeated-measures logistic regression with generalized estimating equations to account for correlated data. Inclusion in this analysis was limited to those subjects who had at least one SH event for which there was at least 12 h of CGM glucose data available from the preceding day. When an additional hypoglycemic event occurred within 3 days after a prior hypoglycemic event, the event was not considered as a new event and was not counted (N = 1). Operating characteristics (sensitivity, specificity, false alarm rate, and positive predictive value [PPV]) are given for various cut points for the four CGM hypoglycemic indices.

RESULTS—One or more SH events occurred in 54 (12%) of the 436 subjects; 36 (8%) subjects experienced one event, 13 (3%) subjects had two events, 4 (0.9%) subjects had three events, and 1 (0.2%) subject had four events. The overall incidence rate of SH was 17.9 events per 100 person-years, being 21.3 in the 160 subjects ≥25 years of age, 16.0 in the 138 subjects 15–24 years of age, and 15.9 in the 138 subjects 8–14 years of age. The rate was 21.5 in the first 6 months of use by the CGM group and 15.0 during the 6 months of CGM use in the control group (which followed the 6-month randomized trial) (P = 0.56). Within the CGM group, there was a trend toward less SH during the second 6 months compared with the first 6 months (8.0 vs. 21.5 events per 100 person-years, respectively; P = 0.02). The clinical characteristics of the 436 subjects are shown in Supplementary Table 1 according to whether or not an SH event occurred during the study.

In a univariate analysis, SH was more likely to occur in subjects who had experienced SH in the 6 months prior to study entry (P < 0.001), and there were suggestive trends for more frequent SH in adults (P = 0.06), females (P = 0.05), subjects with higher scores on the Hypoglycemia Fear Questionnaire (P = 0.02), those with a higher percentage of baseline CGM values ≤70 mg/dL (P = 0.02), and those who had higher glucose variability as assessed with the coefficient of variation (P = 0.08). In general, these factors also were associated with previous SH; consequently, in multivariate analysis only SH during the prior 6 months (hazard ratio [HR] 6.2 [95% CI 3.4–11.6]; P < 0.001) and female sex (2.3 [1.3–4.1]; P = 0.006) (Table 1) were independent predictors of SH during the study. Although the associations of SH during the prior 6 months and female sex with the occurrence of SH were highly statistically significant, the PPV for each was low (42 and 15%, respectively). The occurrence of SH was not associated with baseline HbA_{1c} level. SH occurred in similar proportions of subjects who used an insulin pump and those who used multiple daily injections of insulin.

The second analysis evaluated the predictive value of CGM-measured hypoglycemia during 1 day with the occurrence of SH on the following day. During the full 12 months of follow-up of the CGM group and the last 6 months of follow-up of the control group (the time period during which CGM was used), 48 SH events occurred in 40 subjects. For 31 of the 48 events (65%), CGM was used on the day of the event, which was comparable with a usage rate of 71% on the 11,994 days without an SH event (P = 0.40). For 27 of the 48 events (N = 24 subjects), a sensor was used on the day prior to the event (for at least 12 h). Median percentage of time with glucose levels ≤70 mg/dL was 3% during the 24 h of the calendar day prior to SH compared with 2% of the time on other days (P < 0.001). Although this association was strong statistically, the PPV was extremely low (~5%), and the false alarm rate was extremely high (~95%) even when 30% or more of the glucose values were

Table 1—*Proportional hazards models of baseline factors predictive of SH* (N = *436 subjects who completed the 52-week visit*)**

			Univariate			Initial multivariate*			Final multivariate†		
	N	% SH‡	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
Overall	436	12									
Age (years)					0.06§			0.29§			
8–14	138	10	1.0			1.0					
15–24	138	12	1.2	(0.6–2.5)		0.8	(0.4–1.7)				
≥25	160	14	1.4	(0.7–2.8)		1.0	(0.5–2.0)				
Sex					0.05			0.02			0.006
Male	199	9	1.0			1.0			1.0		
Female	237	15	1.8	(1.0–3.1)		2.2	(1.2–4.1)		2.3	(1.3–4.1)	
n SH events in 6 months prior to study					<0.001			<0.001			<0.001
None	400	10	1.0			1.0			1.0		
≥1	36	42	5.0	(2.8–9.2)		5.5	(2.8–10.6)		6.2	(3.4–11.6)	
Fingersticks per day‖					0.65§						
≤5	135	17	1.0								
6–8	179	8	0.5	(0.2– 0.9)							
≥9	69	13	0.8	(0.4–1.7)							
Insulin delivery					0.70						
Injections	80	14	1.0								
Pump	356	12	0.9	(0.5–1.7)							
HbA_{1c} (%)					0.32§						
<7.0	127	13	1.0								
7.0 to <8.0	197	14	1.1	(0.6–2.1)							
≥8.0	112	9	0.7	(0.3–1.5)							
Hypo Fear Score¶					0.02§			0.46§			
<20	151	8	1.0			1.0					
20 to <30	96	15	1.9	(0.9–4.2)		1.5	(0.7–3.3)				
≥30	184	15	2.0	(1.0–3.9)		1.4	(0.7–2.9)				
% CGM values ≤70 mg/dL (%)#					0.02§			0.75§			
None	25	8	1.0			1.0					
<5	207	9	1.2	(0.3–5.0)		0.9	(0.2–3.8)				
5 to <15	160	16	2.1	(0.5–8.9)		1.2	(0.2–5.6)				
≥15	44	16	2.1	(0.4– 10.2)		1.3	(0.2–8.3)				
Glucose coefficient of variation (%)††					0.08§			0.54§			
<35	116	7	1.0			1.0					
35 to <40	115	13	2.0	(0.8–4.6)		1.9	(0.8–4.5)				
40 to <45	88	16	2.5	(1.0–5.9)		2.4	(0.9–6.2)				
≥45	117	15	2.2	(0.9–5.0)		1.5	(0.5–4.3)				

*Factors with *P* value ≤ 0.20 in univariate model are included in the initial multivariate model. †Factors with *P* value ≤ 0.05 in the initial multivariate model are kept in the final multivariate model. ‡Percentage of subjects with at least one SH event during the study. §*P* value calculated as a continuous variable. Categories are for display purposes in this table. ‖Self-reported number of home glucose meter tests per day. Data collected after study initialization and are therefore missing for 53 subjects. ¶Hypoglycemia Fear Questionnaire (20) consists of 15 5-point Likert scale items, with scores scaled to a 0–100 range. Higher score denotes more fear of hypoglycemia. Missing for five subjects. #CGM data based on blinded use at baseline for approximately 1 week prior to randomization. Results were similar for hypoglycemic AUC and LBGI (12) (data not shown). **Diabetes duration was not associated with SH. Data not shown because this factor was highly confounded with age. ††Coefficient of variation is the SD divided by the mean glucose from the CGM expressed as a percentage.

≤70 mg/dL on the day prior to a SH event (Table 2). Findings were similar for hypoglycemic AUC (0.2 on the day prior to SH vs. 0.1 on other days, $P = 0.002$) and LBGI (1.1 vs. 0.8, $P = 0.003$), with PPVs being low and false-positive rates being high for each (Supplementary Table 2). Results also were similar when assessing the predictive value of 30 consecutive min below 54 mg/dL (Supplementary Table 2). Median glucose was 131 mg/dL on the day prior to an SH event and 141 mg/dL on other days ($P = 0.86$).

CONCLUSIONS—We found the rate of occurrence of SH during the study to be most strongly associated with a history of SH in the 6 months prior to entry into the study. In addition, the rate was higher in females than males. Both of these findings are consistent with prior findings in the DCCT (3,4). As in our study, multivariate analyses conducted on the DCCT data did not identify a predictive model with high sensitivity (3). The incidence rate of SH in this study (17.9 events per 100 person-years) was similar to that of the conventional therapy group in the DCCT (18.7 events per 100 person-years), but significantly lower than the rate in the intensive treatment group (61.2 events per 100 person-years) in the DCCT (Supplementary Fig. 1) (4). A similar SH rate was found in the Sensor-Augmented Pump Therapy for A1c Reduction (STAR) 3 trial (~13 events per 100 person-years in both the CGM group and control group) (14). Our results need to be viewed in the context of the study participants who were well-versed in self-management, were receiving

Table 2—*Sensitivity, specificity, false alarm rates, and PPV of CGM-measured hypoglycemia on 1 day for the occurrence of SH on the following day*

CGM glucose readings ≤70 mg/dL on prior day (%)	*n* of days						
	Total	No SH	SH	Sensitivity*	Specificity†	False alarm‡	PPV§
0	2,009	1,999	10				
>0	3,286	3,269	17	63%	38%	99.5%	0.5%
≤5	3,292	3,278	14				
>5	2,003	1,990	13	48%	62%	99.4%	0.7%
≤15	4,613	4,596	17				
>15	682	672	10	37%	87%	98.5%	1.5%
≤30	5,184	5,162	22				
>30	111	106	5	19%	98%	95.5%	4.5%
All	5,295	5,268	27				

*Sensitivity, Proportion of true SH events where the CGM indices correctly predicted the prior days as positive. †Specificity, Proportion of days without SH where the CGM indices correctly predicted the prior days as negative. ‡False alarm, Proportion of days with CGM indices predicted as positive where there were no SH in the following days. §PPV, Proportion of days with CGM indices predicted as positive where there were SH events in the following days (this is 100% minus the false alarm rate).

intensive insulin management with either an insulin pump or multiple daily injections of insulin, and were performing frequent home blood glucose monitoring.

We also found that CGM-measured hypoglycemia occurred more often on days prior to SH than on other days. However, although the statistical association was strong, the predictive value of biochemical hypoglycemia for subsequent SH was very low. This is because on any given day, SH is a rare event (<1% probability). This probability increases eightfold when more than 30% of CGM values the day prior are in the hypoglycemic range, but there is still less than a 5% chance of SH on the following day. Thus, if a CGM were programmed to sound a warning whenever 30% of values over a 24-h period were ≤70 mg/dL, more than 95% of alarms would be false. The four CGM measures of hypoglycemia studied here (% ≤70 mg/dL, AUC, LBGI, and ≤54 mg/dL for at least 30 consecutive min) are all highly correlated, and results were similar regardless which was used.

One possibility to in part explain the low predictive value could be that subjects modified their diabetes management based on the presence of CGM-measured hypoglycemia, and this reduced their risk of an SH event on the next day. Evidence against this explanation, however, is that during the randomized trial phase of the study, the SH rate in the CGM group was similar to that in the control group (8,9). Another possible factor contributing to the low PPV is measurement error from CGM. Studies of CGM accuracy have shown that the median error during hypoglycemia ranges from 13 to 24 mg/dL (15,16) so that some episodes of true biochemical hypoglycemia are missed by CGM, and some CGM readings in the hypoglycemic range occur when the true glucose concentration is >70 mg/dL.

Kovatchev et al. (17) studied 96 adults with insulin-dependent diabetes and found that history of SH and LBGI calculated from 1 month of home glucose meter data accounted for 40% of the variance of SH episodes over the following 6 months. In another study of 85 adults with type 1 diabetes, Kovatchev et al. (18) reported that LBGI values from home glucose meter data were significantly higher in the 24 h prior to and immediately following an SH episode compared with other days in the same subjects. Cox et al. (19) reported that LBGI was predictive of SH with a sensitivity rate of 58–60% among 100 adults with type 1 diabetes, but did not report the false-positive rate. Our results with CGM data were similar to these studies in that hypoglycemic indices were significantly higher on the day prior to an SH event and that over 50% of SH events could be predicted from these measures depending on the threshold used. However, our data also show a very large false alarm rate (≥95%) when these indices are used to predict SH events. The SH rates in these previous studies, ranging from 192 to 803 events per 100 person-years (17–19), were much larger than that observed in the current study (17.9 events per 100 person-years) and in the DCCT.

In conclusion, the ability to predict the likelihood that SH will occur in the near future remains elusive. The strongest predictor is the occurrence of prior SH. Although biochemical hypoglycemia substantially increases the risk of the occurrence of SH on the next day, SH only occurs in about 1 in 20 days after preceding biochemical hypoglycemia, and thus this is a poor predictor.

Acknowledgments—The study funding was provided by JDRF (grant numbers 22-2006-1107, 22-2006-1117, 22-2006-1112, 22-2006-1123, and 01-2006-8031).

Continuous glucose monitors and sensors were purchased at a bulk discount price from DexCom, Inc. (San Diego, CA), Medtronic MiniMed, Inc. (Northridge, CA), and Abbott Diabetes Care, Inc. (Alameda, CA). Home glucose meters and test strips were provided to the study by LifeScan, Inc. and Abbott Diabetes Care, Inc. The companies had no involvement in the design, conduct, or analysis of the trial or the manuscript preparation.

Below is a listing of relationships of the investigators with companies that make products relevant to the manuscript. Research funds where listed below were provided to the legal entity that employs the individual and not directly to the individual.

B.B. reports having received consulting fees, honoraria, travel reimbursement, and research funds from Medtronic MiniMed, Inc. and grant support from DexCom, Inc. B.A.B. reports having received grant support and serving on the Medical Advisory Board for Medtronic MiniMed, Inc., grant support and a speaker honorarium from Abbott Diabetes Care, Inc., and grant support from DexCom, Inc. C.K. reports having received consulting fees from Medtronic MiniMed, Inc. L.L. reports having received consulting fees and a speaker honorarium from Abbott Diabetes Care, Inc., and consulting fees and research funding from Medtronic MiniMed, Inc. W.V.T. reports having received consulting fees from Medtronic MiniMed, Inc. S.W. reports having received research support, a speaker honorarium and travel reimbursement from Medtronic MiniMed, Inc., and a speaker honorarium from Animas Corp/LifeScan, Inc. No other potential conflicts of interest relevant to this article were reported.

The study was designed and conducted by the investigators. The writing group collectively wrote the manuscript and vouches 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 JDRF, 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.

R.F.-S. researched data, contributed to discussion, wrote the manuscript, and reviewed and edited the manuscript. J.C. contributed to discussion, wrote the manuscript, and reviewed and edited the manuscript. R.W.B. contributed to discussion and reviewed and edited the manuscript. B.B. researched data, contributed to discussion, and reviewed and edited the manuscript. B.A.B. researched data, contributed to discussion, and reviewed and edited the manuscript. H.P.C. researched data, contributed to discussion, and reviewed and edited the manuscript. L.L. researched data, contributed to discussion, and reviewed and edited the manuscript. J.M.L. researched data, contributed to discussion, and reviewed and edited the manuscript. C.K. contributed to discussion and reviewed and edited the manuscript. N.M. researched data, contributed to discussion, and reviewed and edited the manuscript. K.J.R. researched data, contributed to discussion, and reviewed and edited the manuscript. W.V.T. researched data, contributed to discussion, and reviewed and edited the manuscript. S.W. researched data, contributed to discussion, and reviewed and edited the manuscript. D.M.W. researched data, contributed to discussion, and reviewed and edited the manuscript. H.W. researched data, contributed to discussion, and reviewed and edited the manuscript. D.X. contributed to discussion and reviewed and edited the manuscript.

The JDRF CGM Study Group would like to recognize the efforts of the subjects and their families and thanks them for their participation.

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