Prediction of Severe Hypoglycemia

Daniel J. Cox, phd[1]
Linda Gonder-Frederick, phd[1]
Lee Ritterband, phd[1]
William Clarke, md[2]
Boris P. Kovatchev, phd[1]

OBJECTIVE — Prevention of severe hypoglycemia (SH) is premised partially on the ability to accurately anticipate its occurrence. This study prospectively tests methods for predicting SH using blood glucose meter readings.

RESEARCH DESIGN AND METHODS — One hundred adults with type 1 diabetes were followed for 6 months, and 79 insulin-using adults with type 2 diabetes were followed for 4 months. During this time, subjects' routine self-monitored blood glucose (SMBG) readings were stored on and retrieved from memory meters, and participants were queried biweekly about occurrence of SH. Respective demographics for the two groups were age 40.7 and 50.2 years, duration of diabetes 20.0 and 12.2 years, A1C 7.6 and 8.8%, and male sex 43 and 39%, respectively.

RESULTS — Relative risk for SH, quantified by the ratio of an individual's low blood glucose index (LBGI) based on the previous 150 SMBG readings to the LBGI based on recent SMBG readings, increased significantly in the 24 h before SH episodes in individuals with type 1 and type 2 diabetes ($t = 10.3$, $P < 0.0001$, and $t = 4.2$, $P < 0.001$, respectively). A sliding algorithm detected 58% of imminent (within 24 h) SH episodes in the type 1 diabetic group and 60% of those in the type 2 diabetic group when three SMBG readings were available in the 24 h before an episode. Detection increased to 63 and 75%, respectively, if five SMBG readings were available in the 24 h before an episode.

CONCLUSIONS — SH often follows a specific blood glucose fluctuation pattern that is identifiable from SMBG. Thus, partial prediction of imminent SH is possible, providing a potential tool to trigger self-regulatory prevention of significant hypoglycemia.

Diabetes Care 30:1370–1373, 2007

Although achieving the goal of nearly normal glycemia ameliorates much of the risk of hyperglycemia-related complications of diabetes (1–3), achieving such control is often prevented by the occurrence of hypoglycemia, in particular by episodes of severe hypoglycemia (SH), as defined by low blood glucose resulting in stupor, seizure, or unconsciousness that precludes self-treatment (4). Although common in type 1 diabetes, recent evidence suggests that SH can also be problematic for patients with type 2 diabetes treated with insulin (5). Because SH can result in cognitive dysfunction (6–8), accidents, coma, and even death (9), hypoglycemia has been identified as the primary barrier to optimization of glycemic control in diabetes (10,11).

Prevention of SH presumes an individual can either accurately anticipate when such an event is likely to occur to initiate prophylactic steps or detect early signs of mild hypoglycemia to initiate immediate treatment to preclude further progression. The prediction of hypoglycemia has been historically limited to assessment of long-term risk. The Diabetes Control and Complications Trial concluded that only ~8% of the variance of future (within several months) SH episodes could be accounted for from known variables (4). Further studies using a structural equation model history of SH, A1C, hypoglycemia awareness, and autonomic score accounted for 18% of the variance of future SH (12). In a series of previous publications, we reported that the low blood glucose index (LBGI; a measure of the frequency and extent of low self-monitored blood glucose [SMBG] readings) accounts for 40–55% of future (within 6 months) SH episodes (13–16).

Hypoglycemia may lead to a "vicious cycle" of recurrent hypoglycemic episodes (17–21). According to the concept of hypoglycemia-associated autonomic failure (22), recent antecedent hypoglycemia causes defective counterregulation and hypoglycemic unawareness. Hypoglycemia-associated autonomic failure is observed in both type 1 (22) and advanced type 2 (23) diabetes. Considering this, it is reasonable to expect that SH episodes are preceded by specific patterns of hormonal disturbances, which in turn are reflected by specific patterns of glycemic disturbance, potentially recognizable from SMBG. Yet, to the best of our knowledge, prediction of imminent SH in the field had not been reported before our finding of specific glucose patterns preceding SH episodes (24). After this initial report, we took the next logical step toward detection of imminent hypoglycemic episodes, developing a sliding algorithm that uses SMBG data and derivatives from the LBGI to identify patterns of glycemic disturbances likely to be precursors to SH.

With a large prospective study, we tested the hypothesis that a vicious cycle of recurrent low blood glucose can predict imminent SH among individuals with both type 1 and insulin-treated type 2 diabetes using our previously published algorithms. If shown to be prospectively valid, this algorithm has the potential to provide an important clinical tool for the prediction and possible prevention of imminent (within 24 h) SH episodes in type 1 and type 2 insulin-using patients.

From the [1]Department of Psychiatry and Neurobehavioral Sciences, University of Virginia Health System, Charlottesville, Virginia; and the [2]Department of Pediatrics, University of Virginia Health System, Charlottesville, Virginia.

Address correspondence and reprint requests to Daniel J. Cox, PhD, University of Virginia Health System, Box 800137, Charlottesville, VA 22908. E-mail: djc4f@virginia.edu.

Received for publication 3 July 2006 and accepted in revised form 7 March 2007.

Published ahead of print at http://care.diabetesjournals.org on 15 March 2007. DOI: 10.2337/dc06-1386.

Additional information for this article can be found in an online appendix at http://dx.doi.org/10.2337/dc06-1386.

Abbreviations: LBGI, low blood glucose index; SH, severe hypoglycemia; SMBG, self-monitored blood glucose.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Demographic characteristics and SMBG frequency of the participants*

	Type 1 diabetes	Type 2 diabetes
n	90	70
Average age (years)	40.7 ± 11.2	50.2 ± 8.0
Sex (% male)	43	39
Caucasian/African American/Hispanic/Native American (%)	96/3/1/0	71/27/0/2
BMI (kg/m^2)	25.3 ± 4.4	36.3 ± 9.2
Duration of diabetes (years)	20.0 ± 10.7	12.2 ± 8.5
Insulin (units · kg^{-1} · day^{-1})	0.48 ± 0.26	0.56 ± 0.25
A1C (%)	7.6 ± 1.2	8.8 ± 2.0
Number of SH episodes in the last year (average per person)	1.3	0.3
Percent of subjects who experienced at least one SH in the past year (%)	36	10
SMBG readings per day during the study	5.4 ± 2.3	3.5 ± 0.8

Data are means ± SD, unless otherwise indicated.

RESEARCH DESIGN AND METHODS

One hundred adults with type 1 diabetes and 79 adults with type 2 diabetes taking insulin were recruited through regional advertisements. All subjects had been diagnosed for at least 2 years. Exclusion criteria were age >65 years, mental retardation, psychosis, active substance abuse, or significant depression as defined by a Beck Depression Inventory score >16. Ninety subjects with type 1 and 70 with type 2 diabetes completed the entire data collection described below. Table 1 presents demographic data, history of SH, and SMBG frequency of these participants.

All subjects signed institutional review board–approved consent forms and attended orientation meetings where they completed screening questionnaires and had blood drawn for A1C determination. Subjects were introduced to the OneTouch Ultra meter (LifeScan, Milpitas, CA) and were given test strips for 150 SMBG readings. Because the memory of OneTouch Ultra holds 150 readings, subjects notified the researcher when they started their last vial of test strips and a replacement meter was mailed to them along with an additional 150 strips. This ensured an uninterrupted 6-month (4-month for the type 2 diabetic group) sequence of SMBG readings for each subject. Subjects were also introduced to a custom-designed automated e-mail survey system. This system contacted subjects at 2-week intervals and asked them to report occurrence of SH, including the date and time of each episode. SH was defined as severe neuroglycopenia resulting in stupor, seizure, or unconsciousness that precludes self-treatment. Thus, the biweekly surveys contained only symptomatic SH episodes, recorded independently from SMBG. A portion of SH episodes was confirmed via telephone interviews with the subject in order to ensure maximal accuracy of these data. Except for being provided with free SMBG supplies and being asked to report occurrence of SH, no other information (i.e., risk status) or recommendations for changes to the diabetes management routines of the participants were provided. This "no intervention" policy was applied in order to ensure generalization of the results from the study.

Data analysis

After all SMBG and SH surveys were collected, we applied a previously reported sliding algorithm looking for specific blood glucose fluctuation patterns in SMBG data that were shown to precede SH episodes (24). This algorithm involved sliding across the timeline of individual participants' SMBG data and continuously computing whether there was an elevated long-term (last 150 SMBGs) risk of SH occurrence and then superimposing on this long-term risk index whether there was sudden relative increased risk. This increase in imminent risk was defined in one of two ways: *1*) the subject's average LBGI from his/her last 150 SMBG readings was >2.5 (moderate risk), and both the LBGI and its SD increased over the last 50 trials; or 2) the subject's average LBGI from his/her last 150 SMBG readings is >2.5, and the subject has a single sudden low SMBG reading exceeding an individual threshold determined from the subjects' LBGI from the last 150 readings and its SD. If either of these conditions were met, the algorithm indicated an increased risk for imminent SH (e.g., raised a binary "flag" indicating that the following 24 h were risky). To minimize false alarms, the algorithm was individualized so not to signal as risky for imminent SH more than 10% of the total time of the study. The LBGI is central to the computation of risk for imminent severe hypoglycemia. The formulas for the LBGI have been reported previously (15) and are included in their entirety in the online appendix (available at http://dx.doi.org/10.2337/dc06-1386).

To assess the predictive ability of this algorithm, the SMBG data of each subject were matched by date and time to his/her independently reported survey records of SH episodes. Then we counted the percentage of SH episodes preceded by a hypoglycemia flag within <24 h for each subject. Because the algorithm development was finalized before this study (16,24), this entire data collection is a prospective validation of the method. The determination of imminent risk was done after subjects returned their meter; therefore, subjects were unaware of their high-risk periods as quantified by the algorithm.

RESULTS

Frequency of SH

During the study, type 1 diabetic subjects reported a total of 88 SH (0.16 per subject per month) episodes. Twenty percent of type 1 diabetic subjects reported prospective SH in 6 months, whereas 80% reported no episodes. In type 2 diabetic subjects, there were a total of 22 SH episodes (0.08 per subject per month). Ten percent of type 2 diabetic subjects reported prospective SH in 4 months, whereas 90% reported no episodes.

SMBG patterns preceding SH episodes

The clearest indicator of upcoming SH was a highly significant increase in the relative risk for hypoglycemia (e.g., the ratio of LBGI computed over a 24-h period to LBGI computed from the previous 150 SMBG readings). Figure 1 presents the relative imminent SH risk for type 1 and type 2 diabetic subjects. ANOVA with contrasts showed that in type 1 diabetic subjects, the risk ratio (current-to-

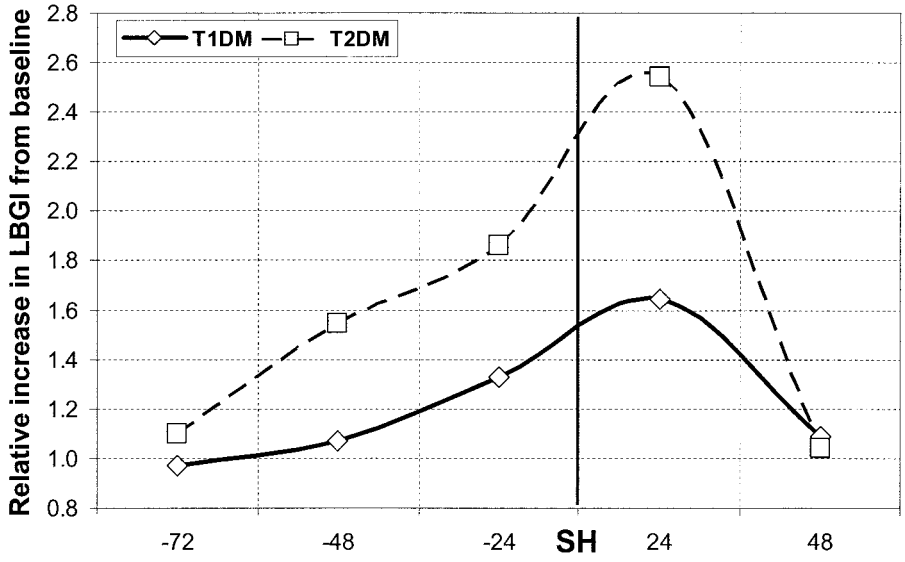

Figure 1— *The ratio of LBGI to its baseline in the 3 days preceding and 2 days following an episode of SH for individuals with type 1 (T1DM) and type 2 (T2DM) diabetes.*

baseline LBGI) increased significantly in the day before SH ($t = 10.3$, $P < 0.0001$). In type 2 diabetic subjects, risk ratio (current-to-overall LBGI) increased significantly over the 2 days preceding an episode ($F = 10.2$, $P < 0.001$), with the most significant increase the day before SH ($t = 4.2$, $P < 0.005$). The relative risk increase in type 2 diabetic subjects was higher than in type 1 diabetic subjects due to a lower baseline risk in the former group, which explains the better prediction of SH in type 2 diabetes.

Prediction of imminent (within 24 h) SH

The percent of survey-reported SH episodes that were predicted by a significant increase in the imminent risk algorithm was then computed. Table 2 presents the accuracy of this short-term prediction for type 1 and type 2 diabetic subjects and shows the percent of predicted episodes when a minimum of three, four, and five SMBG readings (*column 2*) were available in the 24-h period before SH. For example, when four SMBG readings were available for the 24 h in the type 1 diabetic group, 60% of the episodes were predicted. As expected, Table 2 shows that the accuracy of the prediction slightly increases with the number of SMBG readings preceding an episode. For example, if an individual performed three versus five SMBG readings a day, >58 vs. 63% of SH episodes in the type 1 diabetic group and >60 vs. 73% of SH episodes in the type 2 diabetic group could be predicted and potentially avoided. The average warning time between a hypoglycemia imminent risk increase signal by the algorithm and a subsequent episode of SH was 11 h (SD 8.6) in type 1 and 10.8 h (SD 9.1) in type 2 diabetic subjects. Thus, in the majority of cases sufficient warning time for preventative treatment was given.

Table 2—*Prediction of upcoming (within 24 h) SH and mild hypoglycemia*

	Minimum number of SMBG readings in the 24 h preceding the episode	Percent predicted SH episodes
Accuracy in type 1 diabetes	3	58
	4	60
	5	60
Accuracy in type 2 diabetes	3	60
	4	64
	5	73

CONCLUSIONS— Our findings demonstrate that episodes of significant hypoglycemia are often preceded by patterns (signatures) in glucose fluctuations that increase risk for imminent SH. This prospective study also provides evidence for the predictive validity of methods previously developed in our laboratory for short-term risk for significant hypoglycemia. Using a sliding algorithm, we were able to predict 58–60% of imminent (i.e., within the next 24 h) episodes of SH, with only three preceding SMBG readings. When more readings are available, the accuracy of prediction appears to increase. In addition, the accuracy of prediction was somewhat higher in type 2 diabetic subjects. This phenomenon is explained by the significantly lower amplitude and speed of blood glucose fluctuations in type 2 diabetes (25), which result in lower "background noise," thus making the signature of upcoming hypoglycemia more prominent and easier to detect (Fig. 1).

Although these findings provide evidence that patterns in SMBG readings that are precursors to SH can be detected, this study also has some methodological limitations that should be considered. Perhaps the most important is that we do not know if subjects took action, based on their SMBG readings, which affected their risk of SH. Future studies should include measurement of diabetes management behaviors that might reduce or increase risk level. In addition, not all SH episodes were predicted, with the number of unpredicted episodes ranging from 27 to 42%, depending on the number of blood glucose readings available in the preceding 24 h. This suggests that SH is not always preceded by glucose disturbances indicative of increasing risk that occur many hours before the episode, which is not surprising. Risk for SH may also increase suddenly due to other factors, such as overbolusing rapid-acting insulin, skipping or delaying meals, or intense physical activity.

The potential, however, to predict more than half of imminent episodes of SH based on blood glucose meter data has important clinical implications for helping patients to avoid significant hypoglycemia. If online analysis of SMBG data were performed by meters, and early warnings were provided, individuals would be able to take preventives steps to reduce the imminent risk of SH. These steps could include increasing the frequency of SMBG, being more vigilant for any signs of hypoglycemia, reducing insulin dose by 10%, avoiding strenuous exercise without eating extra carbohydrates, and avoiding delayed meals or

missed snacks. This type of online analysis of SMBG data to provide such warnings would be a useful adjunct to other behavioral interventions, such as blood glucose awareness training (26) that focuses on improving detection, treatment, and prevention of extreme blood glucose levels. The next step for clinical investigators is to conduct randomized clinical trials to determine whether patients can use this information to successfully reduce the occurrence of SH. Even though it is unlikely that this predictive algorithm, either alone or in conjunction with behavioral interventions, will completely eliminate SH episodes, this approach may offer a relatively simple and noninvasive method to achieve clinically significant reductions in risk.

Acknowledgments— This study was supported by National Institutes of Heath Grants RO1 DK 28288 and 51562 and by a grant from LifeScan.

References

1. The Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications of insulin-dependent diabetes mellitus. *N Engl J Med* 329:978–986, 1993
2. Reichard P, Phil M: Mortality and treatment side effects during long-term intensified conventional insulin treatment in the Stockholm Diabetes Intervention Study. *Diabetes* 43:313–317, 1994
3. U.K. Prospective Diabetes Study Group (UKPDS): Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. *Lancet* 352:837–853, 1998
4. The Diabetes Control and Complications Trial Research Group: Hypoglycemia in the Diabetes Control and Complications Trial. *Diabetes* 46:271–286, 1997
5. Henderson JN, Allen KV, Deary IJ, Frier BM: Hypoglycemia in insulin-treated type 2 diabetes: frequency, symptoms and impaired awareness. *Diabet Med* 20:1016–1021, 2003
6. Gold AE, Deary IJ, Frier BM: Recurrent severe hypoglycaemia and cognitive function in type I diabetes. *Diabet Med* 10:503–508, 1993
7. Deary IJ, Crawford JR, Hepburn DA, Langan SJ, Blackmore LM, Frier BM: Severe hypoglycemia and intelligence in adult patients with insulin-treated diabetes. *Diabetes* 42:341–344, 1993
8. Lincoln NB, Faleiro RM, Kelly C, Kirk BA, Jeffcoate WJ: Effect of long-term glycemic control on cognitive function. *Diabetes Care* 19:656–658, 1996
9. Bloomgarden ZT: International Diabetes Federation meeting, 1997, and Metropolitan Diabetes Society of New York meeting, November 1997: approaches to treatment and other topics in type 1 diabetes: genetic heterogeneity of diabetes. *Diabetes Care* 21:658–665, 1998
10. Cryer PE: Hypoglycemia: the limiting factor in the management of IDDM. *Diabetes* 43:1378–1389, 1994
11. Cryer PE: Hypoglycaemia: the limiting factor in the glycaemic management of type I and type II diabetes. *Diabetologia* 45:937–948, 2002
12. Gold AE, Frier BM, MacLeod KM, Deary IJ: A structural equation model for predictors of severe hypoglycaemia in patients with insulin-dependent diabetes mellitus. *Diabet Med* 14:309–315, 1997
13. Kovatchev BP, Cox DJ, Gonder-Frederick LA, Clarke WL: Symmetization of the blood glucose measurement scale and its applications. *Diabetes Care* 20:1655–1658, 1997
14. Cox DJ, Kovatchev B, Julian D, Gonder-Frederick LA, Polonsky WH, Schlundt DG, Clarke WL: Frequency of severe hypoglycemia in IDDM can be predicted from self-monitoring blood glucose data. *J Clin Endocrinol Metab* 79:1659–1662, 1994
15. Kovatchev BP, Cox DJ, Gonder-Frederick LA, Young-Hyman D, Schlundt D, Clarke WL: Assessment of risk for severe hypoglycemia among adults with IDDM: validation of the Low Blood Glucose Index. *Diabetes Care* 21:1870–1875, 1998
16. Kovatchev BP, Cox DJ, Kumar A, Gonder-Frederick LA, Clarke WL: Algorithmic evaluation of metabolic control and risk of severe hypoglycemia in type 1 and type 2 diabetes using self-monitoring blood glucose (SMBG) data. *Diabetes Technol Ther* 5:817–828, 2003
17. White NH, Skor DA, Cryer PE, Levandoski L, Santiago JV: Identification of type I diabetic patients at increased risk for hypoglycemia during intensive therapy. *N Engl J Med* 308:485–491, 1983
18. Cryer PE, Gerich JE: Glucose counterregulation, hypoglycemia, and intensive therapy of diabetes mellitus. *N Engl J Med* 313:232–241, 1985
19. Amiel SA, Tamborlane WV, Simonson DC, Sherwin RS: Defective glucose counterregulation after strict glycemic control of insulin-dependent diabetes mellitus. *N Engl J Med* 316:1376–1383, 1987
20. Amiel SA, Sherwin RS, Simonson DC, Tamborlane WV: Effect of intensive insulin therapy on glycemic thresholds for counterregulatory hormone release. *Diabetes* 37:901–907, 1988
21. Cryer PE: Hypoglycemia begets hypoglycemia. *Diabetes* 42:1691–1693, 1993
22. Dagogo-Jack SE, Craft S, Cryer PE: Hypoglycemia-associated autonomic failure in insulin dependent diabetes mellitus. *J Clin Invest* 91:819–828, 1993
23. Segel SA, Paramore DS, Cryer PE: Hypoglycemia-associated autonomic failure in advanced type 2 diabetes. *Diabetes* 51:724–733, 2002
24. Kovatchev BP, Cox DJ, Farhy LS, Straume M, Gonder-Frederick LA, Clarke WL: Episodes of severe hypoglycemia in type 1 diabetes are preceded, and followed, within 48 hours by measurable disturbances in blood glucose. *J Clin Endocrinol Metab* 85:4287–4292, 2000
25. Kovatchev BP, Cox DJ, Gonder-Frederick LA, Clarke WL: Methods for quantifying self-monitoring blood glucose profiles exemplified by an examination of blood glucose patterns in patients with type 1 and type 2 diabetes. *Diabetes Technol Ther* 4:295–303, 2002
26. Cox DJ, Gonder-Frederick LS, Ritterband L, Patel K, Schächinger H, Fehm-Wolfsdorf G, Hermanns N, Snoek F, Zrebiec J, Polonsky W, Schlundt D, Kovatchev B, Clarke W: Blood glucose awareness training (BGAT): what is it, where is it, and where is it going? *Diabetes Spectrum* 19: 43–49, 2006