

Prediction of severe hypoglycemia

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

Additional information for this article can be found in an online appendix at
<http://care.diabetesjournals.org>.

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Running Title: Predicting severe hypoglycemia

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ABSTRACT

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

Research 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-monitoring blood glucose (SMBG) readings were stored on and retrieved from memory meters, and participants were queried bi-weekly about occurrence of SH. Respective demographics for the two groups were: age 40.7/50.2 years, duration of diabetes 20.0/12.2 years, HbA1c 7.6%/8.8%, male gender 43%/39%.

Results: Relative risk for SH, quantified by the ratio of a person's Low BG Index (LBGI) based on the previous 150 SMBG readings to the LBGI based on recent SMBG readings, increased significantly in the 24 hours prior to 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 hours) SH episodes in the type 1 group and 60% of those in the type 2 group when 3 SMBG readings were available in the 24 hours before an episode. Detection increased to 63/75% if 5 SMBG readings were available in the 24 hours before an episode.

Conclusion: SH often follows a specific BG 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.

Introduction

While 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 BG resulting in stupor, seizure, or unconsciousness that precludes self-treatment (4). While common in type 1 diabetes, recent evidence suggests that SH can also be problematic for patients with type 2 diabetes treated with insulin (5). Since SH can result in cognitive dysfunction (6,7,8), 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 DCCT concluded that only about 18% of the variance of future (within several months) SH episodes could be accounted for from a structural equation model using history of SH, HbA_{1c}, hypoglycemia awareness, and autonomic score (12). In a series of previous publications we reported that the Low BG Index* (LBGI, a measure of frequency and extent of low SMBG readings) accounts for 40-55% of future (within 6 months) SH episodes (14,15,16).

Hypoglycemia may lead to a “vicious cycle” of recurrent hypoglycemic episodes (17,18,19,20, 21). According to the concept of hypoglycemia-associated autonomic failure (HAAF, 22), recent antecedent hypoglycemia

causes defective counterregulation and hypoglycemic unawareness. HAAF is observed in both Type 1 (22) and advanced type 2 diabetes (23). 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 prior to our finding of specific glucose patterns preceding SH episodes (26). After this initial report we took the next logical step towards 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 BGs 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 hours) SH episodes in type 1 and type 2 insulin-using patients.

RESEARCH DESIGN AND METHODS

Subjects: One hundred adults with type 1, and 79 adults with type 2 diabetes taking insulin, were recruited through regional advertisement. All subjects had been diagnosed for at least two years. Exclusion criteria were age >65, 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.

Procedure: All subjects signed IRB-approved consent forms and attended orientation meetings where they completed screening questionnaires and had blood drawn for HbA_{1c} determination. Subjects were introduced to the OneTouch Ultra™ meter (LifeScan Inc., Milpitas, CA) and were given test strips for 150 SMBG readings. Since the memory of OneTouch Ultra™ holds 150 readings, subjects notified the researcher when they started their last vial of test strips and then 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 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 two-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 bi-weekly 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 BG-fluctuation patterns in SMBG data that were shown to precede SH episodes (26). 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 greater than 2.5 (moderate risk) **and** both the LBGI and its standard deviation increase over the last 50 trials; or 2) The subject’s average LBGI from his/her last 150 SMBG readings is greater than 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 standard deviation. 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 hours were risky. In order 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 (Low BG Index) 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 Appendix (available at <http://care.diabetesjournals.org>).

In order 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 less than 24 hours for each subject. Since the algorithm development was finalized prior to this study (16, 26), this entire data collection is a prospective validation of the method. Since the determination of imminent risk was done after subjects returned their meter, subjects were unaware of their high risk periods as quantified by the algorithm.

RESULTS

Frequency of SH: During the study type 1 subjects reported a total of 88 SH (0.16 per subject per month). Twenty percent of type 1 subjects reported prospective SH in six months while 80% reported no episodes. In type 2 subjects there were a total of 22 SH episodes (0.08 per subject per month). Ten percent of type 2 subjects reported prospective SH in four months, while 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 LBG1 computed over a 24-hour period to LBG1 computed from the previous 150 SMBG readings. Figure 1 presents the relative imminent SH risk for type 1 and type 2 subjects. Analysis of variance with contrasts showed that in type 1 subjects, the risk ratio (current-to-baseline LBG1) increased significantly in the day prior to SH ($t=10.3$, $p<0.0001$). In type 2 subjects risk ratio (current-to-overall LBG1) increased significantly over the 3 days preceding an episode ($F=10.2$, $p<0.001$), with the most significant increase the day prior to SH ($t=4.2$, $p<0.005$). The relative risk increase in type 2 subjects was higher than in type 1 subjects due to a lower baseline risk in the former group, which explains the better prediction of SH in type 2

Prediction of imminent (within 24 hours) 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 (Table 2A) and type 2 subjects. (Table 2B), and shows the percent of predicted episodes when a minimum of three, four, and five SMBG readings (column 2) were available in the 24-hour period prior to SH. For example, when four SMBG readings were available for the 24 hours in the type 1

group, 60% of 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 a person performed 3 vs 5 SMBG readings a day, more than 58 vs. 63% of SH episodes in the type 1 group, and more than 60 vs 73% of episodes in the type 2 group could be predicted and potentially avoided.

Insert Table 2 about here

The average warning time between a hypoglycemia imminent risk increase signal by the algorithm and a subsequent episode of SH was 11 hours ($SD=8.6$) in type 1 and 10.8 hours ($SD=9.1$) in type 2 subjects. Thus, in the majority of cases sufficient warning time for preventative treatment was given.

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 hours) 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 subjects. This phenomenon is explained by the significantly lower amplitude and speed of BG fluctuations in type 2 diabetes (29), which result in lower “background noise,” thus making the signature of upcoming hypoglycemia more prominent and easier to detect (Figure 1).

While 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 number of unpredicted episodes ranging from 27 to 42%, depending on the number of BG readings available in the preceding 24 hours. This suggests that SH is not always preceded by glucose disturbances indicative of increasing risk that occur many hours prior to the episode, which is not surprising. Risk for SH may also increase suddenly due to other factors, such as over-bolusing 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 BG meter data has important clinical implications for helping patients to avoid significant hypoglycemia. If on-line analysis of SMBG data were performed by meters, and early warnings provided, individuals would be able to take preventives steps to reduce 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 on-line analysis of SMBG data to provide such warnings would be a useful adjunct to other behavioral interventions, such as Blood Glucose Awareness Training (30) that focuses on improving detection, treatment and prevention of extreme BGs. 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 non-invasive method to achieve clinically significant reductions in risk.

ACKNOWLEDGMENTS

This study was supported by NIH grants RO1 DK 28288 and 51562 and by a grant from LifeScan Inc, Milpitas, CA.

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Table 1: Demographic characteristics and SMBG frequency of the participants.

	T1DM (N=90)	T2DM (N=70)
Average (SD) age in years	40.7 (11.2)	50.2 (8.0)
Gender: % Male	43%	39%
% Caucasian/ African American / Hispanic / Native American	96 / 3/ 1 /0	71 / 27 / 0 / 2
Body mass index	25.3 (4.4)	36.3 (9.2)
Duration of diabetes (years)	20.0 (10.7)	12.2 (8.5)
Insulin units/kilogram/day	0.48 (0.26)	0.56 (0.25)
HbA _{1c}	7.6 (1.2)	8.8 (2.0)
Average per person # of SH episodes in the last year	1.3	0.3
% 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)

Table 2: Prediction of upcoming (within 24 hours) SH and MH.

A: Accuracy in T1DM		% Predicted SH Episodes
Minimum number of SMBG readings in the 24 hours preceding the episode.	3	58%
	4	60%
	5	60%
B: Accuracy in T2DM		% Predicted SH Episodes
Minimum number of SMBG readings in the 24 hours preceding the episode.	3	60%
	4	64%
	5	73%

FIGURE LEGENDS

Figure 1: Average BG (upper panel) and Low BG Index (lower panel) 3 days preceding and 3 days following an episode of severe hypoglycemia for individuals with T1DM (open triangles) and T2DM (open squares) illustrating

