

Assessment of Risk for Severe Hypoglycemia Among Adults With IDDM

Validation of the low blood glucose index

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OBJECTIVE — To evaluate the clinical/research utility of the low blood glucose index (LBGI), a measure of the risk of severe hypoglycemia (SH), based on self-monitoring of blood glucose (SMBG).

RESEARCH DESIGN AND METHODS — There were 96 adults with IDDM (mean age 35 ± 8 years, duration of diabetes 16 ± 10 years, HbA_{1c} $8.6 \pm 1.8\%$), 43 of whom had a recent history of SH (53 did not), who used memory meters for 135 ± 53 SMBG readings over a month, and then for the next 6 months recorded occurrence of SH. The SMBG data were mathematically transformed, and an LBGI was computed for each patient.

RESULTS — The two patient groups did not differ with respect to HbA_{1c} , insulin units per day, average blood glucose (BG) and BG variability. Patients with history of SH demonstrated a higher LBGI ($P < 0.0005$) and a trend to be older with longer diabetes duration. Analysis of odds for future SH classified patients into low- (LBGI < 2.5), moderate- (LBGI 2.5–5), and high- (LBGI > 5) risk groups. Over the following 6 months low-, moderate-, and high-risk patients reported 0.4, 2.3, and 5.2 SH episodes, respectively ($P = 0.001$). The frequency of future SH was predicted by the LBGI and history of SH ($R^2 = 40\%$), while HbA_{1c} , age, duration of diabetes, and BG variability were not significant predictors.

CONCLUSIONS — LBGI provides an accurate assessment of risk of SH. In the traditional relationship history of SH-to-future SH, LBGI may be the missing link that reflects present risk. Because it is based on SMBG records automatically stored by many reflectance meters, the LBGI is an effective and clinically useful on-line indicator for SH risk.

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Severe hypoglycemia (SH), defined as a low blood glucose (BG) resulting in stupor, seizure, or unconsciousness that precludes self-treatment (1), is a serious threat to patients with IDDM. Although most SH episodes are not fatal, there remain numerous negative sequelae leading to compromised occupational and scholastic functioning, social embarrassment, poor

judgment, serious accidents, and possible permanent cognitive dysfunction (2–4). The more distressing the SH episode, the greater the psychological fear of hypoglycemia (5), and this fear can lead to avoidance behaviors that result in poor metabolic control (6). Although intensive therapy can prevent or delay the development of long-term complications associ-

ated with diabetes (7,8), the threat and fear of SH can significantly discourage patients and health care providers from pursuing such therapy. Consequently, hypoglycemia has been identified as the major barrier to improved metabolic control (9).

Various approaches to assess the risk of SH have been tested, including low HbA_{1c} (10,11), intensive therapy (7,8,12), inadequate hormonal counterregulation (13–15), hypoglycemia unawareness (11,16–18), and a history of SH (1,10,11). The Diabetes Control and Complications Trial (with intensive therapy) demonstrated that only ~7% of future SH could be predicted from known variables (1). A recent structural equation model accounted for 18% of the variance of SH using history of SH, hypoglycemia awareness, and autonomic score (11). These studies consistently demonstrated that only a modest percentage of future SH can be accounted for on the basis of traditional predictors, and that history of SH is the best indicator of future SH.

However, as a predictor of future SH risk, history of SH has three major disadvantages: 1) it may cause a sense of inevitability of future SH, thus discouraging patients from pursuing intensive therapy; 2) as a measure it is too slow, i.e., it may not reflect within a reasonable time a patient's increased vulnerability for upcoming SH; and 3) it cannot indicate a decrease in SH risk. These disadvantages make tracking of SH episodes an unreliable and inconvenient way for evaluating changes in diabetes management. The same is true for tracking the state of hypoglycemia awareness.

Thus, pursuing better prediction of future SH, we need to struggle not only for a larger percentage of explained SH variance, but also for better predictors, capable of serving as on-line measures for SH risk, i.e., able to identify in real time increased or reduced risk for SH. Ideal data for the computation of such measures are provided by memory meters that store multiple BG records. The problem, however, is extracting the relevant information for SH from these records.

In a previous publication (19), we proposed a logarithmic-type BG data transfor-

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Abbreviations: ANOVA, analysis of variance; BG, blood glucose; LBGI, low blood glucose index; SH, severe hypoglycemia; SMBG, self-monitoring of blood glucose.

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

mation that symmetrizes the BG measurement scale. While the immediate utility of this transformation was primarily theoretical, providing an appropriate statistical background for BG data analysis, the more advanced applications of transforming BG data have sound clinical and research applications. The transformed data serve as a base for defining the low blood glucose index (LBGI), a measure that has been shown to be associated with SH risk (20). The current manuscript evaluates the utility of the LBGI in assessing the risk of future SH. We hypothesize that although a history of SH may predict future SH episodes, this relationship is mediated by the current status of low BG control, which can be quantified by the LBGI (Fig. 1).

RESEARCH DESIGN AND METHODS

Subjects

The inclusion criteria for participants in this study were: having IDDM for at least 2 years, taking insulin since the time of diagnosis, and routinely performing self-monitoring of blood glucose (SMBG) with a meter more than twice daily. The participants were recruited through newsletters, notices posted in diabetes clinics, and direct physician referral. Of 100 initially recruited patients, 96 met the inclusion criteria and completed all data collection phases. Of these patients, 43 reported at least two episodes of SH in the past year (SH group), and 53 patients reported no such episodes during the same period (NoSH group). There were 65 patients who were from central Virginia, 17 from Baltimore, Maryland, and 14 from Nashville, Tennessee; there were 38 men and 58 women. The mean age was 35 ± 8 years, mean duration of disease 16 ± 10 years, mean insulin units per kilogram per day 0.58 ± 0.19 , and mean total glycosylated hemoglobin (HbA_{1c}) $8.6 \pm 1.8\%$. The nondiabetic range for the glycosylated hemoglobin assay in our laboratory is 4.4–6.9%. According to a previously published criterion (17), 58 patients were classified as hypoglycemia aware, while 38 patients had reduced awareness.

Procedure

All patients attended orientation meetings, were informed about the study, signed consent forms, and completed questionnaires asking for demographic and diabetes-related parameters, including the number of SH episodes in the previous 12 months.

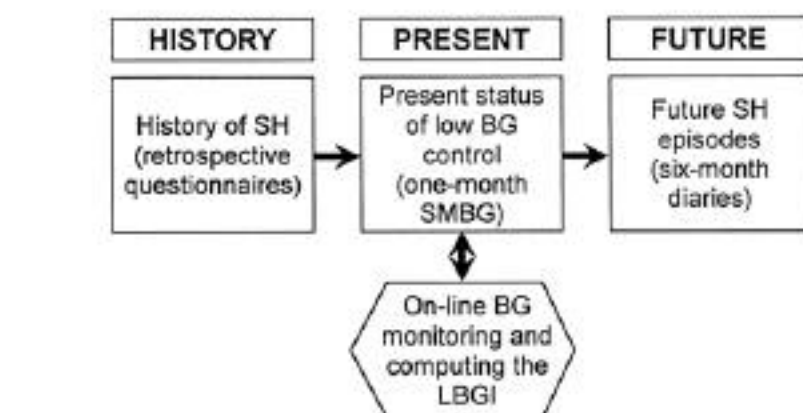


Figure 1—The relationship between history of SH and future SH is mediated by the present status of low BG control, which can be quantified by the LBGI.

These retrospective estimates of SH were validated in telephone interviews with patients' spouses or significant others. Then patients' personal meters were exchanged for LifeScan One Touch II memory meters and SMBG supplies (LifeScan, Milpitas, CA). Patients were instructed in use of the meters and asked to measure their BG 2–5 times a day for 1 month. Upon completing this 1-month SMBG session, a glycosylated hemoglobin assay was performed, and the patients' BG readings were electronically transferred from the memory meters into a personal computer using standard software available from LifeScan. This resulted in an average of 135 ± 53 readings per patient. All but nine patients measured their BG more than twice daily, the smallest data sample had 53 SMBG readings over 30 days. For the next 6 months, patients recorded date and time of occurrence of all SH episodes (stupor, seizure, or unconsciousness that precludes self-treatment) on diary sheets that were mailed in monthly. Patients were instructed to telephone the investigators whenever an SH episode occurred, which triggered a structured interview concerning events leading up to and immediately following the episode in question. In all cases, these interviews confirmed that an event of SH had in fact occurred. This information was used for verification of patient diaries. During the study, patients continued with their routine medical management by their own physician. In no way did their participation in the study interfere with this routine. We were able to document that during the 6-month prospective period, only one person shifted from subcutaneous insulin injections to pump therapy, and one other patient shifted from a routine regimen to an

intensive therapy. Both subjects were from the NoSH group.

LBGI

The LBGI is a summary statistic, extracted from a series of SMBG data, that increases when the frequency and/or the extent of low BG readings increase. Thus, a higher LBGI may indicate a record of numerous mild low BGs, a few extreme low BGs, or a mixture of both. In other words, the LBGI combines in a single number the percentage of low BG readings and their magnitude in the lower BG range. The LBGI is based on a previously reported BG scale transformation (19), and the mathematics behind this transformation and the LBGI are presented in an appendix to that previous report. In general, to compute a patient's LBGI, his or her BG readings are first weighted as follows: readings >6.25 mmol/l receive zero weights and readings ≤ 6.25 mmol/l are assigned progressively increasing weights, with the highest being 100 at a BG = 1.1 mmol/l. Then the LBGI is computed as the average weight of all SMBG readings. Formally, the SMBG readings are transformed first, using one of the following two formulas:

$$\text{Transformed BG} = 1.794 \times \{[\log(\text{BG})]^{1.026} - 1.861\},$$

if BG is measured in millimoles per liter, or

$$\text{Transformed BG} = 1.509 \times \{[\log(\text{BG})]^{1.084} - 5.381\},$$

if BG is in milligrams per deciliter.

This makes the transformed BG symmetric around zero, ranging from $-10^{1/2}$ to $10^{1/2}$ (19). Then, a risk value is assigned to each SMBG reading as follows:

Table 1—Group comparisons between patients with and without a history of SH

	SH group	No SH group	t	P
Age	37.3 ± 8.9	33.5 ± 6.6	2.3	0.025*
Duration of diabetes	18.4 ± 10.0	14.3 ± 9.9	2.0	0.05*
HbA _{1c}	8.4 ± 1.7	8.7 ± 1.9	—	NS
Insulin (U · kg ⁻¹ · day ⁻¹)	0.60 ± 0.19	0.56 ± 0.18	—	NS
Average BG (mmol/l)	8.2 ± 1.8	8.5 ± 1.9	—	NS
BG variance (mmol/l)	4.3 ± 1.0	3.8 ± 1.1	2.5	0.013*
% Hypoglycemia aware‡	37	79	Z = 4	<0.001†
LBGI	5.2 ± 3.3	2.9 ± 1.8	4.2	<0.0005†

Data are means ± SD or %. *Trend: P between 0.01 and 0.05; †significant at P = 0.01; ‡nonparametric Mann-Whitney comparison was used.

If Transformed BG is <0, Risk (BG) = 10 × (Transformed BG)², otherwise Risk (BG) = 0.

Finally, the LBGI is computed as the mean of these risk values across all SMBG readings (19,20). An example of an LBGI calculation based on three BG readings is given below. A detailed description and software code for this calculation are available from the authors of this article.

Example

Suppose that we have the following BG readings for a hypothetical patient: 2.6, 7.8, and 4.4 mmol/l. The transformed BGs that correspond to these readings are -1.6, 0.4, and -0.66, respectively. According to the formulas above, the first and the third transformed BGs result in risk values of 25.6 and 4.4, respectively, while the second reading results in a risk value of zero, since the transformed BG is positive. The LBGI is computed as the average of these three risk values, i.e., LBGI = 10 for this patient. Note that three readings are insufficient to calculate a patient's LBGI; this issue is discussed in CONCLUSIONS.

RESULTS

History of SH and LBGI

Table 1 summarizes the results of comparisons of patients with and without a recent history of SH (SH and NoSH groups) on several parameters: age, duration of diabetes, insulin units per day per kilogram, HbA_{1c}, average BG, BG variability (as quantified by the mean and SD of 1 month of SMBG readings), hypoglycemia awareness, and LBGI. The significance level of the tests was adjusted for multiple comparisons; a result was considered significant if its P value was <0.01 and a trend if this level was between 0.01 and 0.05. The two groups did

not differ in terms of HbA_{1c}, average BG, or insulin units per day. Patients with a history of SH demonstrated a trend to be older, with longer diabetes duration and more variable BG (Ps between 0.01 and 0.05). There were 37% of SH patients and 79% of NoSH patients who were hypoglycemia aware (Z = 4.0, P < 0.001). Patients with a history of SH had a significantly higher LBGI than patients with no such history: 5.2 vs. 2.9 (t = 4.2, P < 0.0005).

A 2 × 2 (SH-NoSH × aware-reduced aware) analysis of variance (ANOVA) demonstrated that hypoglycemia-reduced aware subjects had somewhat higher LBGIs (5.7 vs. 4.2 for the SH group and 3.1 vs. 2.9 for the NoSH group), but this effect was not significant (F = 2.4, P = 0.13).

Relationship between history of SH and future SH episodes, mediated by the LBGI

Table 2 presents the relationship between the reported number of SH episodes in the

past year and the observed number of SH episodes during the 6 months of diaries, with the LBGI as a variable mediating between past and future SH. The table includes 3 × 3 cells, based on patients' history of SH and prospective SH episodes. The three retrospective categories were as follows: 0, 1–6, and >6 SH episodes in the past year. The three prospective categories were similar: 0, 1–3, and >3 SH episodes in the following 6 months. Each cell presents the row-percentage of patients that fell in that cell and their average LBGI. A 3 × 3 ANOVA confirmed that the LBGI significantly differentiates the cells (F = 6.5, P < 0.001 for the main effects).

LBGI thresholds and risk categories for SH

Using the dependence between the LBGI and the odds ratio (21) for a subsequent SH, we identified two naturally occurring LBGI thresholds. This was done by computing the SH odds ratio at a number of LBGI cutoff values, starting at LBGI = 1.5, as follows: for each LBGI cutoff value, we computed how many times patients who have LBGIs above this value are more likely to have a future SH than patients with LBGIs below that value. Figure 2 presents the odds ratio plotted against LBGI cutoff values from 1.5 to 6.5 with an increment of 0.25.

For example, patients who have LBGIs >3.5 are four times more likely to experience future SH than patients who have LBGIs <3.5, or similarly, patients who have LBGIs >6.3 are six times more likely to experience future SH than patients who have LBGIs <6.3 (Fig. 2). Plotting the odds ratio against the LBGI identified two LBGI

Table 2—Relationship between history of SH and future SH episodes, mediated by the LBGI

	n	Prospective SH episodes (6 months)		
		0	1–3	>3
n	—	65	15	16
Retrospective SH episodes (1 year)				
0	53	96	4	0
% of patients		2.8	3.4	—
LBGI				
1–6	24	46	37	17
% of patients		3.6	5.7	5.3
LBGI				
>6	19	16	21	63
% of patients		4.0	4.4	6.7
LBGI				

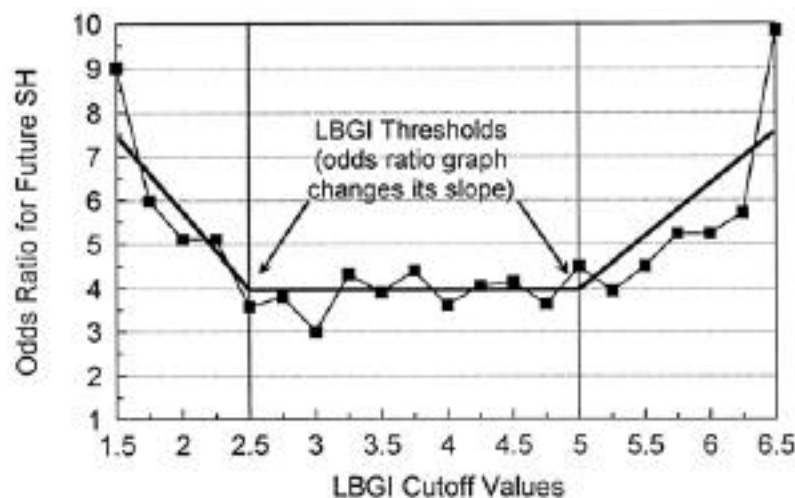


Figure 2—Odds ratios for a future SH along LBG1 cutoff values. The estimated odds ratios are plotted by linked squares. The thick black line presents a linear approximation of these estimates. The odds ratio at each LBG1 cutoff value shows how many times patients who have an LBG1 above that value are more likely to experience a future SH compared with patients whose LBG1 is below that value. Natural LBG1 thresholds are identified by the points at which the odds ratio graph changes its slope.

thresholds, 2.5 and 5, where the odds ratio graph changes its slope. Figure 2 demonstrates that, initially, the likelihood of a subsequent SH decreases from 9 to 4 as LBG1 reaches 2.5. Then the odds ratio levels off at a value of 4, stays flat until LBG1 reaches 5, and increases steeply after that. Thus, LBG1 = 2.5 and LBG1 = 5 are the two LBG1 thresholds where the likelihood for a subsequent SH sharply changes. These thresholds identify three SH risk categories: low- (LBG1 <2.5), moderate- (LBG1 between 2.5 and 5), and high-risk (LBG1 >5).

Prediction of the frequency of future SH episodes

In the subsequent 6 months, patients in low-, moderate-, and high-risk categories reported 0.4, 2.2, and 5.2 SH episodes, respectively (Fig. 3). Kruskal-Wallis non-parametric ANOVA demonstrated that these frequencies are significantly different ($\chi^2 = 13.3$, $P = 0.001$).

Regression analysis was conducted to determine which variable would significantly predict future occurrence of SH. First, six variables were sequentially forced into the model: HbA_{1c}, number of retrospective SH episodes in the past year, age, duration of diabetes, variability of BG, and LBG1. Then a standard backward elimination of the non-significant predictors was performed. Table 3 presents the changes in R^2 and the significance of each of these variables. The final regression model included two predictive variables (history of SH and LBG1) and was

highly significant ($F = 30$, $P < 0.0001$), accounting for 40% of the variance of SH episodes in the subsequent 6 months. It demonstrated that 1) LBG1 made a significant contribution to the prediction of future SH even when all potential predictors of SH were already entered into the model; 2) a detailed history of SH was the only traditional predictor significantly related to future SH; and 3) HbA_{1c}, age, duration of diabetes, and variability of BG were not related to prospective SH, accounting in combination for only 4% of SH variance. These results confirmed our previous findings (20) and the findings of other investigators (11). Awareness of hypoglycemia had no separate contribution (in addition to history of SH) to prediction of future SH and was not included in this model because it is a categorical variable.

Furthermore, we used the history of SH as a categorical yes/no variable and restricted our analysis to patients who had a history of SH (SH group). For this patient group, the LBG1 was the only significant predictor of future SH ($F = 32$, $P < 0.0001$, $R^2 = 43\%$). The regression was through the origin, i.e., had a nonsignificant constant term that was set to zero. This analysis is to be applied when detailed records of previous SH episodes are not available, i.e., when it is only known that a patient has or has not a history of SH.

Finally, an exploratory analysis confirmed our notion that the LBG1 was capable of differentiating patients at risk for imminent SH from patients at risk for a future, but not imminent, SH, while the additional risk factors, including history of SH, are of little value for such on-line SH risk assessment. We compared patients who reported SH within 3 months of the LBG1 calculation with those who reported SH during months 4–6 but did not report SH within the first 3 months. The LBG1 of the first subgroup was 6.4, versus 3.5 for the second subgroup ($P = 0.005$). The two subgroups reported similar numbers of retrospective SH episodes in the last year: 9.6 and 7.6 ($P = 0.5$), and did not differ in HbA_{1c}, age, or duration of diabetes. This suggests that high-risk status reflects the likelihood of an SH event sooner than later.

CONCLUSIONS—SH occurs as a consequence of a specific combination of numerous interacting biological and behavioral risk factors, such as inadequate counterregulation, intensive therapy, low HbA_{1c}, reduced hypoglycemic awareness, inattention, and inappropriate self-treatment (22). Each of these factors follows a complex (and often untraceable) temporal pattern, and the between-factor interactions are

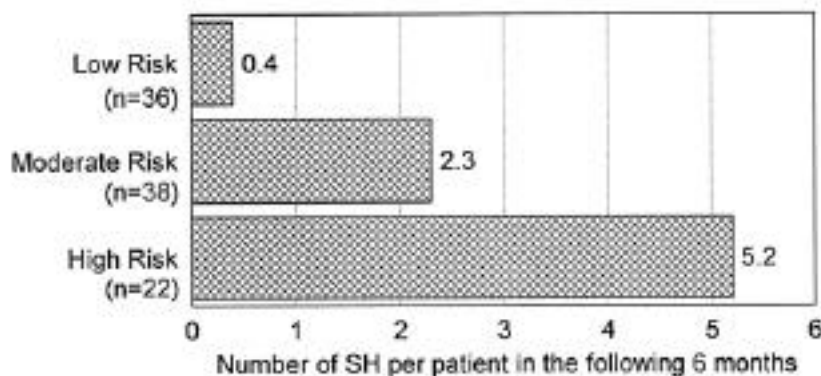


Figure 3—Prospective SH for patients in low-, moderate-, and high-risk categories.

Table 3—Prediction of future SH in the subsequent 6 months

Step	Variable	R ²	R ² change	Significance
Sequential forced entry of potential predictors				
1	HbA _{1c}	1	1	0.3
2	Number of SH episodes in the past year	32	31	<0.001
3	Age	35	3	0.2
4	Duration of diabetes	36	1	0.2
5	BG variability	36	0	0.5
6	LBGI	44	8	<0.001
Backward elimination of nonsignificant predictors				
1	HbA _{1c}	44	0	0.9
2	Duration of diabetes	43	1	0.3
3	BG variability	42	1	0.2
4	Age	40	2	0.1

Data are %.

rather enigmatic. As a result, a prediction of SH based on just a few factors would be modestly accurate, as evidenced by studies that accounted for 7–18% of SH variance (1,11). On the other hand, an attempt to incorporate numerous factors and their interactions would require complicated models and demanding data collection that would preclude such an approach from practical and clinical application.

This study examines and validates the LBGI, a new approach to quantifying both the frequency and extent of low BG readings, which is capable of extracting on-line information about future SH from SMBG data. The LBGI is based on the following logical sequence of ideas: 1) SH can be predicted from observation of patients' BG fluctuations, i.e., by tracking patients' BG control system at a macro level, without a reference to specific underlying factors; 2) such macro-level tracking information is available through SMBG and is stored by memory meters; and 3) the problem is to develop statistical methods for extracting information relevant to SH from SMBG.

In a previous analysis, based on 50 SMBG readings/patient collected over 2–3 weeks by 78 IDDM patients, the LBGI accounted for 33% of the variance of SH (20). The results of the current study are consistent with these previous findings, but are at the same time more precise, since the present SMBG data are improved in two respects: 1) now we have, on average, 135 readings per patient over 4–5 weeks and 2) the data are transferred directly from patients' memory meters, which reduces

the probability for errors. While the improved data lead to better prediction of future SH (R² = 40%), key characteristics remained reliable across the two studies: 1) the mean LBGI of patients without SH problems was 2.8 in our previous data (20) and is 2.9 in our current data set (Table 1) and 2) in our previous study, we concluded that an optimal threshold LBGI value was 2.25, but "additional research is needed to determine if an LBGI of 2.25, 2.4 or 2.8 will be the optimal critical value" (20). Our current data confirm that the threshold between low and moderate SH risk is at LBGI = 2.5 (Fig. 1). In addition, split-half analysis of our current data demonstrated high internal reliability of LBGI: 3.9 ± 2.8 vs. 3.9 ± 3.2 in the first versus the second half of memory meter data, with a correlation of 0.82 (P < 0.001).

As any other statistic, the LBGI depends on the way the data are collected, and this may sometimes lead to inaccurate conclusions. For example, if SMBG readings are taken only at certain times of day (when BG is low), this would artificially elevate the LBGI, overpredicting the risk for a subsequent SH. Or, if measurements are done only during euglycemia or hyperglycemia, this may artificially decrease the LBGI, underestimating the risk for SH. Thus, for a correct assessment of SH vulnerability, it is important for the SMBG readings to approximate patients' temporal BG fluctuations as accurately as possible. Theoretically, such approximation will be most precise if multiple SMBG readings are randomly spread over a period of time.

Future data and analyses are needed to identify optimal strategies of taking daily SMBG readings.

Our current data demonstrate that ~130 SMBG readings, spread over 4–5 weeks, are sufficient to permit the calculation of an accurate LBGI. This index has been shown to be reliable, internally and across studies, and to be a significant predictor of future SH. It can be used separately or in combination with a history of SH (number of previous SH episodes or simply SH-NoSH classification). In addition, the computation of a patient's LBGI is quite uncomplicated, which encourages its clinical and research use. For example, the LBGI can be easily calculated using any spreadsheet or statistical software that provides data transformations, including Microsoft Excel, SASS, S-plus, etc. Thus, clinicians and researchers can use a familiar software and SMBG data format to perform these computations. We anticipate that in the future, the calculation of patients' LBGI could be incorporated directly into memory meters in the same way that contemporary meters calculate average BG. A patient's LBGI exceeding a critical value would then be used as an on-line alert for increased risk for SH.

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