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Risk Analysis of Blood Glucose Data: A Quantitative Approach to Optimizing the Control of Insulin Dependent Diabetes

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Patients with Insulin-Dependent Diabetes are continuously involved in a clinical optimization process: to maintain strict glycemic control without increasing their risk for hypoglycemia. This study offers quantitative tools for on-line assessment of the quality of this optimization, based on self-monitoring of blood glucose (SMBG). Ninety-six adults with Insulin Dependent Diabetes Mellitus (IDDM), age 35 ± 8 yrs., duration of diabetes 16 ± 10 yrs., HbA_{1c} $8.6 \pm 1.8\%$, 43 of whom had a recent history of severe hypoglycemia (SH), while 53 did not, used Lifescan One Touch II meters for 135 ± 53 SMBG readings over a month. For the following six months the subjects recorded occurrence of SH. The two patient groups, with and without a history of SH, did not differ in age, duration of diabetes, HbA_{1c}, insulin units/day, average BG or BG variability. We suggest a computational procedure based on a symmetrization of the BG measurement scale and on a superimposed BG risk function, that allows for computation of two glycemic control markers: the Low BG Index (LBGI) and the High BG Index (HBGI). The LBGI is associated with SH: the LBGI and the rate of change of the BG risk, classified correctly 77% of the subjects with vs. without a history of SH and accounted for 46% of the variance of future SH. The HBGI, in combination with age, duration of diabetes and daily insulin dose, accounted for 57% of the variance of patients' glycosylated hemoglobin. We conclude that the LBGI and the HBGI are accurate on-line SMBG measures for patients' glycemic control.

Keywords: Glycemic control, hypoglycemia, hyperglycemia, self-monitoring of blood glucose (SMBG)

In health the blood glucose (BG) level is internally regulated through insulin release from the pancreas that counterbalances carbohydrate intake from food, drinks, etc. Since patients with Insulin Dependent Diabetes Mellitus (IDDM) are unable to produce sufficient amounts of insulin, this internal self-regulation is disrupted. The standard daily control of IDDM involves multiple insulin injections, which lower BG. However, this external BG control is still not nearly as good as the internal self-regulation: too little insulin results in chronic high BG levels, too much can cause hypoglycemia. Recent studies demonstrated that the most effective long-term control of IDDM

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is the strict maintenance of BG levels within a normal range through intensive insulin therapy. Detailed results of its effects are presented by the Diabetes Control and Complications Trial Research Group (DCCT) (1993) and its European counterpart (Reichard and Phil, 1994): chronic high BG levels were proven to cause many complications in multiple body systems over time, while too much insulin resulted in hypoglycemia. Without immediate treatment hypoglycemia can rapidly progress to severe hypoglycemia (SH), a condition defined as an episode of neuroglycopenia which precludes self-treatment and requires external help for resuscitation (DCCT Research Group, 1997). On one side, intensive therapy is the best long-term treatment of IDDM, on the other it was associated with at least a threefold increase in SH (Reichard and Phil, 1994; DCCT Research Group, 1997). Since SH could result in accidents, coma and even death, it discourages patients and health care providers from pursuing intensive therapy. Consequently, hypoglycemia has been identified as the major barrier to improved glycemic control (Cryer, 1993; Cryer, Fisher and Shamoon, 1994). In short, patients with IDDM face a life-long clinical optimization problem: to maintain strict glycemic control without increasing risk for hypoglycemia. A bio-mathematical problem, associated with this optimization is to create a measure, based on multiple BG readings that quantifies both trends: towards chronically high BG levels and towards increased risk for hypoglycemia.

Traditionally, patients' glycemic control is assessed through measurement of glycosylated hemoglobin (HbA_1 or HbA_{1c}), an accepted biochemical marker for average BG levels over the preceding two months (Svendsen *et al.*, 1982; Santiago, 1993). High glycosylated hemoglobin is associated with chronically high BG levels and therefore, this measure sets the reference standard for control of BG with respect to hyperglycemia. However, HbA_{1c} was repeatedly proven to be ineffective for assessment of patients' risk for hypoglycemia (DCCT Research Group, 1991; Gold *et al.*, 1997; Cox *et al.* 1994). In fact, the DCCT concluded that only about 7% of future SH episodes can be predicted from known variables, including HbA_{1c} (DCCT Research Group, 1997), and this prediction was improved to 18% using a recent structural equations model (Gold *et al.*, 1997). The reason for that poor prediction is quite understandable — HbA_{1c} reflects the average BG level over a few weeks preceding the measurement, but is not sensitive to the relatively quick and sharp BG transitions in the lower BG range that are responsible for SH. In a previous publication we reported that a new risk measure, the Low BG Index, based on a normalizing transformation of BG data (Kovatchev *et al.*, 1997), can predict 40% of future SH episodes (Kovatchev *et al.*, 1998).

In this manuscript we offer a numerical approach to the clinical optimization problem related to IDDM, based on the following idea: The struggle for tight glycemic control often results in great BG fluctuations over time. This process is influenced by many external factors, including the timing and amount of insulin injected, food eaten, physical activity, etc. In other words, fluctuations of the BG level over time are the measurable result of the action of a complex dynamic system, influenced by many internal and external factors. Observed at a macro-level, such a system has a random behavior, which includes quick transitions (such as SH episodes) to extreme areas of its state space. An appropriate evaluation of stationary and non-stationary characteristics of this random process would identify measures for both chronically high and very low BG levels, as well as a measure for the overall glycemic control of the patient. In order to be clinically useful, these markers need to be computed on readily available data through relatively simple algorithms. In order to be clinically proven, these markers need to correlate with established glycemic control measures, such as HbA_{1c}, and be sensitive to the risk for upcoming SH.

We will first derive from a set of clinical assumptions a skewness-correction transformation for BG data. Then, on that basis, we will suggest a BG risk function and two related statistics: the Low and High BG Indices. To incorporate the temporal behavior of

the system we introduce two statistics, related to the rate of change of the BG risk: the indices *SDn* and *SUp*, which are measures of how fast the BG risk function increases and decreases, respectively. All indices will be computed from memory meter data, automatically stored during routine home BG self-monitoring. We will refer to previous reports and reanalyze existing data to validate our data transformation, evaluate the relationship between the Low BG Index, *SUp* and *SDn* and hypoglycemia and between the High BG Index and patients' glycosylated hemoglobin. We will conclude that the Low and High BG Indices offer numerically comparable assessments of the risk for hypoglycemia and hyperglycemia, respectively, that can be combined in a single measure of overall glycemic control.

RESEARCH DESIGN AND METHODS

Subjects

Ninety-six individuals, 58 women and 38 men, who had IDDM for at least two years and were taking insulin since the time of diagnosis were recruited through advertisement in newsletters, diabetic clinics, and through direct referrals. All subjects were routinely using self-monitoring devices to measure their BG. Their average age at the time of recruitment was 35 years (SD = 8), the average duration of diabetes was 16 years (SD = 10) and the average daily insulin dose was 0.58 units per kilogram (SD = 0.19). Since the goal of this research was to study risk factors for SH, subjects who had problems with recurrent SH were preferentially recruited. History of SH was recorded as the number of SH episodes in the previous year. The preferential recruitment resulted in 43 participants who reported having at least two SH episodes in the previous year, and 53 who reported none. These two groups will be referred to as SH and No SH in the text. The SH group included 45% of all subjects, which is greater than the estimated 4% to 22% frequency of IDDM patients who have problems with SH (DCCT, 1997). Consequently, the incidence of SH in this study was high compared to reports from population-based studies.

Procedure

After an initial screening assessment, the subjects' usual BG meters were replaced by Lifescan One-Touch II memory meters that can store up to 250 BG readings. The study proceeded with one month of home self-monitoring of BG (SMBG) that yielded on average 135 BG readings per subject (SD = 53). At one-month meetings the participants' BG data were downloaded for analysis and blood was drawn for HbA_{1c} determination. The average glycosylated hemoglobin was 8.6, SD = 1.8%. During the following six months all participants recorded in diaries occurrence of moderate or severe hypoglycemia. These diaries were mailed in monthly and resulted, on average, in 2.3 records of SH episodes per subject (SD = 4.8). SH occurred predominantly in subjects from the SH group who reported 4.8 (SD = 7.0) SH episodes on average.

Symmetrization of the BG Measurement Scale

The BG levels are measured in mg/dl in the USA and in mmol/L (or mM) most elsewhere. Throughout this paper we employ the mM scale. The two scales are directly related by: 18 mg/dl = 1 mM. The whole range of most BG reference meters is 1.1 to 33.3 mM, which is considered to cover practically all observed values. According to the recommendations of the DCCT (1993), the target BG range for a person with IDDM is considered to be 3.9 to 10 mM. Hypoglycemia is identified as a BG below 3.9 mM, hyperglycemia is a BG above 10 mM. It is obvious that this scale is not symmetric — the hyperglycemic range (10 to 33.3 mM) is much greater that the hypoglycemic range (1.1–3.9 mM) and the euglycemic range (3.9–10 mM) is not centered within the scale. As a result the numerical center of the scale (17.2 mM) is distant from its "clinical center" — the clinically desired clustering of the BG values of patients with diabetes around 6–6.5 mM. In a previous report we suggested that

this asymmetry of the scale leads to skewed distributions of patients' BG readings, and suggested a scale transformation that corrects the problem (Kovatchev *et al.*, 1997). The mathematics of this transformation is based on two clinical assumptions: **A1**) The transformed whole BG range should be symmetric around zero. **A2**) The transformed target BG range should be symmetric around zero. In other words, let $f(BG)$ be a continuous function defined on the BG range [1.1, 33.3] that has the general two-parameter analytical form

$$f(BG, \alpha, \beta) = [(\ln(BG))^{\alpha} - \beta], \alpha, \beta > 0$$

that satisfies the conditions **A1:** $f(33.3, \alpha, \beta) = -f(1.1, \alpha, \beta)$ and **A2:** $f(10, \alpha, \beta) = -f(3.9, \alpha, \beta)$. The logarithmic form of $f(BG, \alpha, \beta)$ is intuitively justified by the fact that the BG level is a concentration of sugar in the blood, and therefore would have a generally logarithmic presentation. In the discussion we will also see that this form can be deduced from the classic Box-Cox skewness correction transformation (Box and Cox, 1964), if we impose the assumptions **A1** and **A2**. By multiplying by a third parameter γ we fix the minimal and maximal values of the transformed BG range at $-\sqrt{10}$ and $\sqrt{10}$ respectively. These values are convenient for two reasons: first, a random variable with a central normal distribution would have 99.8% of its values within the interval $[-\sqrt{10}, \sqrt{10}]$, and second, this provides a nice calibration of the BG risk function from 0 to 100 (see the next section). This scaling and the assumptions **A1** and **A2** lead to the equations

$$(\ln(33.3))^{\alpha} - \beta = -[(\ln(1.1))^{\alpha} - \beta]$$

$$(\ln(10.0))^{\alpha} - \beta = -[(\ln(3.9))^{\alpha} - \beta]$$

$$\gamma \cdot [(\ln(33.3))^{\alpha} - \beta] = -\gamma \cdot [(\ln(1.1))^{\alpha} - \beta] = \sqrt{10}$$

which are easily reduced to a single nonlinear equation for the parameter α. When solved numerically under the restriction $\alpha > 0$, it gives: $\alpha = 1.026$, $\beta = 1.861$ and $\gamma = 1.794$[†].

Figure 1 presents the graph of $f(BG) = 1.794\,[(\ln(BG))^{1.026} - 1.861]$. The whole BG range is transformed into the symmetric interval $[-\sqrt{10}, \sqrt{10}]$. The target BG range is transformed into the symmetric interval $[-0.9, 0.9]$. Since $f(6.25) = 0$, the transformation brings together (and sets to zero) the numerical and the clinical center of the BG scale.

The BG Risk Function

After fixing the parameters of $f(BG)$ depending on the measurement scale that is being used, we define the quadratic function $r(BG) = 10.f(BG)^2$.

[†] If BG is measured in mg/dl, by replacing in the equations 33.3 mM by 600 mg/dl, 1.1 mM by 20 mg/dl, 10 mM by 180 mg/dl, and 3.9 mM by 70 mg/dl, we obtain $\alpha = 1.084$, $\beta = 5.381$, $\gamma = 1.509$.

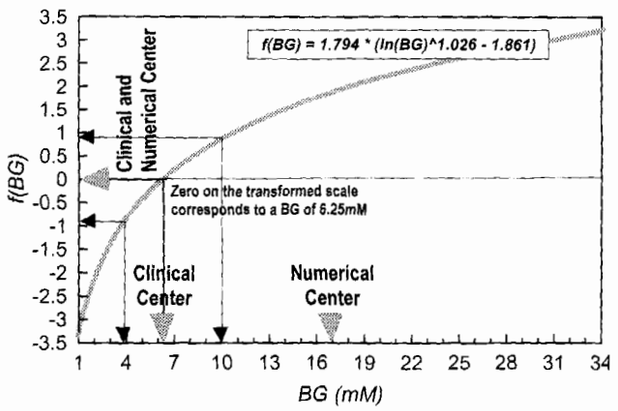

FIGURE 1 Transforming the blood glucose: the whole BG range and the target BG range are transformed into symmetric around zero intervals. The hypoglycemic and hyperglycemic ranges become symmetric. The numerical and the clinical center of the scale coincide after the transformation and are equal to zero.

Figure 2A presents the graph of $r(BG)$ over the transformed hypoglycemic, target and hyperglycemic BG ranges. Figure 2B presents $r(BG)$ in the original BG scale.

The function $r(BG)$ ranges from 0 to 100. Its minimum value is achieved at BG = 6.25 mM, a safe euglycemic BG reading, while its maximum is reached at the extreme ends of the BG scale. Thus, $r(BG)$ can be interpreted as a measure of the risk associated with a certain BG level. The left branch of this parabola identifies the risk of hypoglycemia, while the right branch identifies the risk of hyperglycemia. Based on that, we define the Low and the High BG Indices as follows:

Let $x_1, x_2, \ldots, x_n$ be n BG readings of a subject and let

$rl(BG) = r(BG)$ if $f(BG) < 0$ and 0 otherwise;

$rh(BG) = r(BG)$ if $f(BG) > 0$ and 0 otherwise.

The Low Blood Glucose [Risk] Index (LBGI) and the High BG [Risk] Index (HBGI) are then defined as:

$$\text{LBGI} = \frac{1}{n}\sum_{i=1}^{n} rl(x_i) \text{ and}$$

$$\text{HBGI} = \frac{1}{n}\sum_{i=1}^{n} rh(x_i) \text{ respectively.}$$

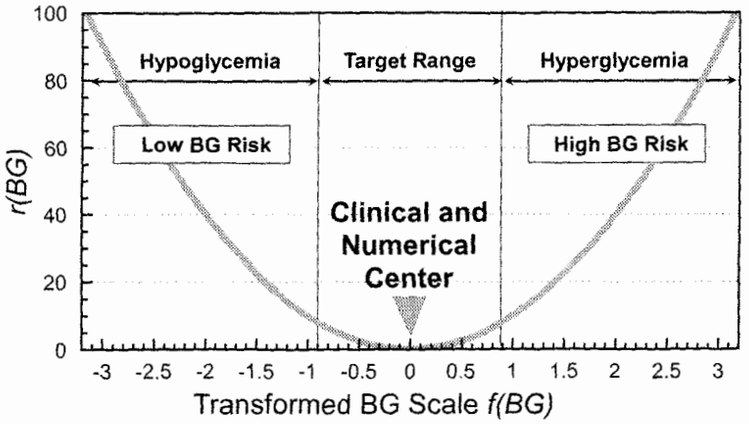

FIGURE 2a The blood glucose risk function as defined on the transformed BG scale. The values of $r(BG)$ at the left part of the scale (the Hypoglycemic range) are referred to as Low BG Risk, while the values at the right part of the scale (the Hyperglycemic range) are referred to as High BG Risk.

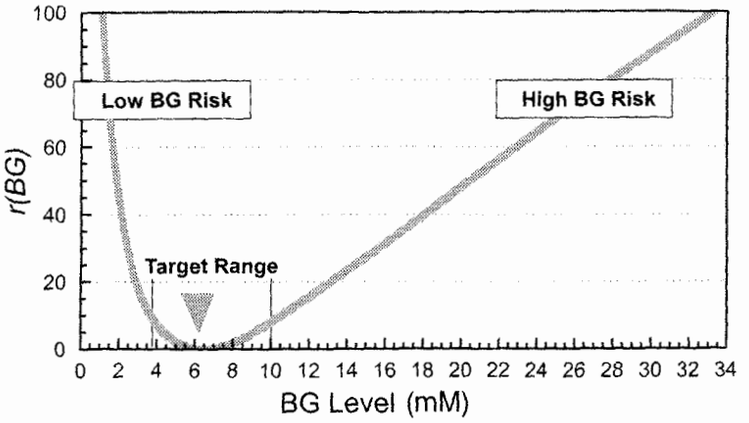

FIGURE 2b The blood glucose risk function plotted over the standard BG scale.

In other words, the LBGI is a non-negative quantity that increases when the number and/or extend of low BG readings increases. Similarly, the HBGI increases when the number and/or extend of high BG readings increases. The sum of LBGI + HBGI has a theoretical upper limit of 100.

RESULTS

BG Scale Transformation

The scale transformation $f(BG)$ was applied to all 96 memory meter data sets. A Kolmogorov-Smirnov test was used to fit a normal distribution to each individual sample. With a significance level of 0.01, only five out of 96 hypotheses that a normal distribution fits the transformed data were rejected. By the same criteria, the transformed data had a closer to normal distribution than the original BG readings in 70 out of 96 cases. This confirms our previous report in which $f(BG)$ normalized 203 out of 205 individual BG data sets (Kovatchev *et al.*, 1997).

Low BG Index

The LBGI was previously used to differentiate subjects with and without a history of SH and to predict future SH episodes. We demonstrated that the LBGI is one of the best predictors of future SH accounting (in combination with history of SH) for 40% of the variance of future SH episodes (Kovatchev *et al.*, 1998). Now, with these data, we computed the LBGI for each subject and estimated the speed of BG risk changes in the lower BG range (BG < 6.25 mM) as follows: We first transformed the memory meter data of each subject using the function $f(BG)$. Then cubic splines were used to interpolate the transformed readings and to produce estimates of $f(BG)$ at one-hour increments. Based on this interpolation we estimated *SDn* as the average change of $rl(BG)$ within one hour when BG goes down, and *SUp* as the average change of $rl(BG)$ within one hour when BG goes up (Thus, *SDn* is positive, while *SUp* is negative, since in the lower BG range the risk function increases as BG goes down). For more details on the calculation of *SDn* and *SUp* and some related comments *see* the Appendix.

Retrospectively, age, duration of diabetes, HbA_{1c}, insulin units/day, average BG and BG variability (defined as the standard deviation of the BG readings) did not differentiate SH from NoSH subjects. A t-test demonstrated that subjects with a history of SH had significantly higher LBGI, 5.2 (SD = 3.3) vs. 2.0 (SD = 1.8), $t = 4.2$, $p < 0.001$. The rate of BG risk changes *SDn* and *SUp* were also greater (by absolute value) for the SH group, 2.5 (SD = 1) vs. 1.9 (SD = 0.9) and −2.5(SD = 1.1) vs. --1.8(SD = 0.8), both $p's < 0.01$, indicating sharper risk transitions in the low BG range. A significant discriminant model (Chi-square = 22.5, $p < 0.0001$) using the three variables LBGI, *SDn* and *SUp* classified correctly 77% of the subjects with vs. without a history of SH.

Prospectively, a significant regression model ($F = 17.5$, $P < 0.0001$) using LBGI, *SDn*, *SUp* and history of SH had an $R^2 = 46\%$, e.g. accounted for 46% of the variance of future SH. This represents a 6% increase over our previous report (Kovatchev *et al.*, 1998) based on LBGI and history of SH. Both *SDn* and *SUp* had a significant contribution to this classification/prediction that is linearly independent from LBGI and SH history. No other variables (e.g. HbA_{1c}, age, diabetes duration, HBGI, etc.) had any additional contribution.

High BG Index

As it was to be expected, the HBGI was significantly correlated with patients' glycosylated hemoglobin, $r = 0.7$, $p < 0.001$. A significant regression model ($F = 29$, $p < 0.0001$) using HBGI, age, duration of diabetes and patients' daily insulin dose accounted for 57% of the variance of HbA_{1c}. HBGI was the most significant variable of this regression, $t = 10.0$, $p < 0.0001$. The relationship between the HBGI and HbA_{1c} was approximately linear, approximated with a piecewise line with two cutpoints, HBGI = 4.5 and

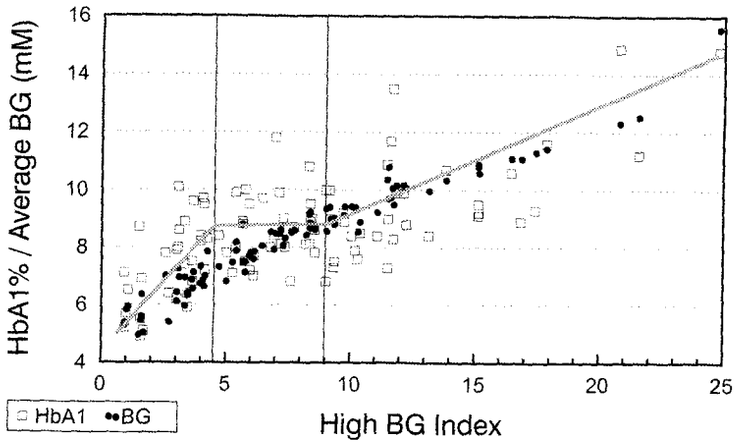

FIGURE 3 Relationships between average BG, HbA_{1c} and High BG Index.

HBGI = 9 that marked changes in the slope of the relationship (Figure 3).

Based on these cutpoints we identify three high BG risk zones: HBGI < 4.5, HBGI between 4.5 and 9 and HBGI above 9. This is similar to the procedure we previously reported for the LBGI — the risk for SH was classified within three zones LBGI < 2.5, LBGI between 2.5 and 5 and LBGI above 5 (Kovatchev *et al.*, 1998). These classifications allow for an assessment of the overall glycemic control of a patient with IDDM, based on memory meter data.

Table I is constructed as follows: Vertically we present the three SH risk groups based on the LBGI, horizontally we present the high BG risk groups, based on HBGI. In each cell of the table we present four numbers: the average (per subject) number of retrospectively/prospectively reported SH episodes, average HbA_{1c} and the number of subjects.

TABLE I Glycemic Control Evaluation Based on LBGI and HBGI

		HBGI		
		<4.5	4.5–9.0	>9.0
LBGI	<2.5	SH: 0/0 8.3%/n = 7	SH: 1.2/0.1 8.9%/n = 9	SH: 1.4/0.7 9.9%/n = 20
	2.5 – 5.0	SH: 2.3/0 7.3%/n = 6	SH: 4.9/2.2 8.6%/n = 20	SH: 4.4/3.6 9.5%/n = 12
	>5.0	SH: 4.7/4.3 7.0%/n = 17	SH: 15.3/5.7 8.0%/n = 3	SH: 15.0/12.0 7.6%/n = 2

It is intuitively clear that the patients in cell (1,1) should have the best glycemic control. Indeed, these seven subjects reported 0 SH episodes (retrospectively and prospectively) and had HbA_{1c} = 8.3%. As expected, the glycosylated hemoglobin increases horizontally from left to right and the number of SH episodes increases vertically from top to bottom. 3 × 3 ANOVA demonstrated that all three variables significantly differed between the cells of Table I: History of SH, $F = 6.7$, $p < 0.001$; Prospective SH episodes, $F = 4.0$, $p = 0.005$; HbA_{1c}, $F = 9.6$, $p < 0.001$. However, LBGI was not a significant effect for the glycosylated hemoglobin and HBGI was not a significant effect for the number of prospective SH episodes.

DISCUSSION

This investigation offers quantitative tools for studying the clinical optimization problem for improvement in glycemic control without increasing the risk of SH. In general, there are two mathematical approaches to that problem. The first approach would be to build a deterministic model of insulin-glucose dynamics in subjects with IDDM and evaluate individual parameters of the dynamics with the goal to assess subjects' ability to process glucose, counterregulate and avoid SH, etc. Computer freeware for interactive simulation of insulin and BG

profiles, such as AIDA, has been developed on the basis of a simple insulin-glucose model (Lehmann, 1999). We reported previously a deterministic model of insulin-glucose-counter-regulation dynamics during controlled hyperinsulinemic clamp (Kovatchev *et al.*, 1999) that demonstrated that NoSH subjects have more aggressive counterregulatory response, thus greater self-protection against SH.

The second approach would be to observe subjects' metabolic system on a "macro-level," without a reference to specific underlying factors, by simply recording multiple BG readings and trying to establish patterns through stochastic modeling. The assumption behind this second approach is that SH and high glycohemoglobin are two extremes of BG irregularity, associated with IDDM and driven by behavioral and biological factors. Some of these factors contribute to future SH, while others are precursors to high glycosylated hemoglobin. The problem then is to develop statistical methods capable of extracting from SMBG information relevant to SH and glycosylated hemoglobin. Our first step in that direction was to derive and validate a symmetrization of the BG measurement scale, since it was our opinion that the asymmetry of the scale prevents the standard statistical procedures from adequate assessment of fluctuations in the low BG range. The reason for that is simply numerical-compared to hyperglycemia, the range of hypoglycemia is several times smaller and therefore most averaging procedures would be intrinsically biased. To correct that we suggested a logarithmic transformation based on widely accepted clinical assumptions. The general logarithmic form of $f(BG)$ can be derived from the classic Box-Cox power transformation $(x^a - 1)/a$, $a > 0$, widely used for correction of skewed data (Box and Cox, 1964) as follows: Let $g(x; a, b) = (x^a - 1)/a - b$, where for right-skewed data (like BG levels) the parameter $a < 1$. By fitting the parameters of $g(x; a, b)$ to satisfy the assumptions **A1** and **A2**, we find that the parameter a should be very close to zero. On the other hand, $\lim_{a \to 0}(x^a - 1)/a = \ln(x)$, which suggests that a skewness correction satisfying **A1** and **A2** should be of a logarithmic type. This being said, we will emphasize one more time that the transformation $f(BG)$, unlike the Box-Cox skewness correction, does not depend on a particular data set. Instead, its parameters are evaluated on the basis of accepted clinical assumptions. This makes it applicable to a variety of data sets without a parameter re-estimation. The transformation $f(BG)$ makes the BG measurement scale symmetric around zero. An immediate statistical implication is that the distribution of most BG data sets that we examined becomes closer to normal. Thus, the assumptions of the parametric statistical tests will be better satisfied with transformed, rather than the original BG data. Clinically, the transformed data indicate the quality of a subjects' glycemic control: a mean less than zero shows a tendency towards hypoglycemia during the measurements, while a mean above zero is associated with hyperglycemia. A large standard deviation implies poor glycemic control, a small standard deviation shows a tight range for the BG levels. This intuitive idea serves as a basis for the definition of the LBGI and HBGI — two risk statistics related to the individual glycemic control in the low and high BG range.

The LBGI repeatedly proved to be the most powerful predictor of SH. By using the rates of risk change *SDn* and *SUp* we include a temporal component in our considerations. This new model improves the prediction of future SH episodes, accounting for 46% of the variance of future SH episodes — 6% up from our previous report (Kovatchev *et al.*, 1998, Cox *et al.*, 1994). As we mentioned in the introduction, this result is substantially better than the prediction of SH by other models. Although we collected data about all symptomatic low BG episodes experienced by the subjects, we concentrated our predictive analyses on SH for two reasons: 1) SH is a clinically significant complication of IDDM that is identified by a clear objective criteria, while milder hypoglycemia is symptom perception-dependent, and 2) SH is traditionally difficult to predict.

The HBGI is associated with patients' glycosylated hemoglobin. However, this association is no stronger than the association with HbA_{1c} of

the average BG, or $(2.07 \times [averageBG^{0.596}])$ as originally suggested by Svendsen *et al.* (1982). With our data, both these quantities had correlations of 0.7 with HbA_{1c}, i.e. displayed relationship similar to the linear relationship of HBGI with HbA_{1c}. The major advantage of using HBGI instead of simply the average BG is that its values are comparable to LBGI. In other words, we now have measures for both low and high BG risk that are compatible, comparable and additive (the two indices are defined on non-intersecting sets of BG readings — below and above 6.25). In addition, the HBGI describes very well the average BG — their relationship is almost strictly linear (see Figure 3), and their correlation in these data was 0.98. The latter offers one more confirmation of the fact that in calculations using the standard BG scale, such as taking the mean BG, the hypoglycemic readings simply vanish due to the asymmetry of the scale. It also offers one more explanation of the poor prediction of SH from average BG and HbA_{1c}.

Clinically, LBGI and HBGI offer an assessment of patients' glycemic control that covers both the risk for hypoglycemia and the risk for hyperglycemia. This assessment uses readily available self-monitoring data and a simple computational procedure that can be incorporated in self-monitoring devices, or in their downloading software. However, further research is needed to establish clinically accurate target limits and low/high risk zones for the LBGI and HBGI. Since LBGI and HBGI quantify observed BG fluctuations, their values depend on a variety of biologic and behavioral factors such as awareness of hypoglycemia, treatment decisions and strategies, individual choices, etc. Consequently the control of LBGI and HBGI within target limits is possible through a variety of means, including adjustments of regiment, awareness training, etc.

APPENDIX: COMPUTATION OF BG RISK RATE OF CHANGE

Let $x_1, x_2, \ldots, x_n$ be n BG readings of a subject's meter at time points $t_1, t_2, \ldots, t_n$. We transform this data by calculating the numbers $f(x_1), f(x_2), \ldots, f(x_n)$ and draw a cubic spline $S(t)$ passing through the points $(t_1, f(x_1))$, $(t_2, f(x_2))$, $\ldots$, $(t_n, f(x_n))$. Thus, the function $S(t)$ is a continuous function defined on the whole interval $[t_1, t_n]$ and such that $S(t_j) = f(x_j)$, for $j = 1, \ldots, n$. We calculate the numbers

$$s_k = 10.S(k + t_1)^2 \text{ if } S(k) < 0 \text{ and } 0 \text{ otherwise;}$$
$$\text{for } k = 0, 1, \ldots, t_n - t_1$$

thus getting interpolated values of $rl(BG)$ at one-hour increments.

Next, consider all couples of numbers S_k with consecutive indices: $C_0 = (s_0, s_1)$, $C_1 = (s_1, s_2)$, $C_2 = (s_2, s_3)$, ... and denote by M_{up} the set of all couples C_k, such that $s_k > s_{k+1}$ and by M_{dn} the set of all couples C_k, such that $s_k < s_{k+1}$. Finally, let SDn be the average of the numbers $s_{k+1} - s_k$, provided that $C_k \in M_{dn}$, and SUp be the average of the numbers $s_{k+1} - s_k$, provided that $C_k \in M_{up}$.

In fact, the numbers SDn and SUp provide a measure for the rate of change of $r(BG(t))$ as BG fluctuates in the lower BG range. More precisely, SDn is a certain measure estimating the rate of increase of $rl(BG(t))$ while BG goes down and SUp is a measure estimating the rate of decrease of $rl(BG(t))$ while BG goes up.

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