Hypoglycemia Risk and Glucose Variability Indices Derived from Routine Self-Monitoring of Blood Glucose Are Related to Laboratory Measures of Insulin Sensitivity and Epinephrine Counterregulation

Achilleas N. Pitsillides, Ph.D.,¹ Stacey M. Anderson, M.D.,² and Boris Kovatchev, Ph.D.¹

Abstract

Background: The widely held assumptions that in type 1 diabetes glucose variability may correlate with insulin sensitivity and impaired epinephrine counterregulation have not been studied directly. Here we investigate possible relationships between outpatient measures of glucose variability and risk for hypoglycemia with physiological characteristics: insulin sensitivity and hypoglycemia counterregulation.

Methods: Thirty-four subjects with type 1 diabetes (14 women, 20 men; 37 ± 2.1 years old; glycosylated hemoglobin [HbA1c], $7.6 \pm 0.21\%$) performed self-monitoring of blood glucose (SMBG) for a month, followed by an inpatient hyperinsulinemic euglycemic and hypoglycemic clamp. SMBG field data were used to calculate measures of glucose variability and risk of hypoglycemia, while the clamp procedure was used to evaluate insulin sensitivity and epinephrine response during induced hypoglycemia. Spearman partial correlations adjusted for age, duration of diabetes, body mass index, gender, and HbA1c were used to assess the relationship between the field indices of glucose variability and the physiological characteristics of diabetes.

Results: Two glucose variability measures correlated positively ($P < 0.01$) with insulin sensitivity: the Average Daily Risk Range (ADRR) ($\rho = 0.5$) and the Glycemic Lability Index ($\rho = 0.48$). The Low Blood Glucose Index, a measure of the risk for hypoglycemia, and the ADRR correlated negatively with maximum epinephrine response during hypoglycemia: $\rho = -0.46$, $P < 0.01$ and $\rho = -0.4$, $P = 0.03$, respectively.

Conclusions: Higher insulin sensitivity and lower epinephrine response during hypoglycemia are related to increased glucose variability (as quantified by the ADRR), irrespective of HbA1c and other patient characteristics. Lower epinephrine relates to risk for hypoglycemia as well.

Introduction

GLUCOMETERS ARE AN INTEGRAL PART of diabetes management and care, providing real-time self-monitoring of blood glucose (SMBG), as well as easy access to the history of SMBG, to patients and physicians. However, these features maybe underutilized:¹ for example, long-term (e.g., 1-month) SMBG data, while sparse in comparison to continuous glucose monitoring (CGM) data, can capture sufficient details of the patient's glucose profile to be useful for assessment of overall glucose variability and risk for hypoglycemia. In particular, a recent study has shown that high glucose variability calculated from SMBG data is a risk factor for peripheral neuropathy in type 1 diabetes patients.² Risk-based measures estimated from SMBG data, such as the Low Blood

Glucose (BG) Index (LBGI) and the Average Daily Risk Range (ADRR), were validated as predictors of future episodes of severe hypoglycemia, better than glycosylated hemoglobin (HbA1c) alone.^{3,4}

It is also well established that the main obstacle to achieving normoglycemia through insulin therapy is iatrogenic hypoglycemia.⁵ Hypoglycemia and counterregulation have been studied extensively, and it is known that the main defense in patients with type 1 diabetes against falling BG concentrations is increased adrenomedullary epinephrine, which is often impaired.^{5,6} Moreover, recent antecedent iatrogenic hypoglycemia could cause both defective counterregulation and hypoglycemia unawareness, referred to as hypoglycemia-associated autonomic failure.⁷ Even without recent episodes, lower epinephrine response during sleep has been

Departments of ¹Psychiatry and Neurobehavioral Sciences and ²Medicine/Endocrinology, University of Virginia, Charlottesville, Virginia. This study has clinical trial registration number NCT00943787 at clinicaltrials.gov.

associated with increased risk for non-symptomatic nocturnal hypoglycemia and was concluded that sleep impairs counterregulatory hormone responses to hypoglycemia, which may contribute to increased risk for hypoglycemia.⁸⁻¹⁰ However, both hypoglycemia unawareness and impaired epinephrine response have been shown to be potentially reversible by avoidance of hypoglycemia for as little as 2-3 weeks.^{11,12}

Less studied is the potential relationship between SMBG profiles and physiological characteristics of the patient, such as insulin sensitivity and hypoglycemia counterregulation. Insulin sensitivity, i.e., the rate of insulin action on glucose uptake,^{13,14} is an important quantity in diabetes management and care, serving as a base for the calculation of insulin dosing as well as other treatment parameters. While it is intuitive that those patients with higher insulin sensitivity would be more susceptible to increased glucose variability, to date no studies have examined directly the relationship between field parameters of glucose control accessible via routine SMBG data and insulin sensitivity as measured during a hyperinsulinemic euglycemic clamp procedure.¹⁴ Furthermore, even though the hypoglycemia-prediction power of ADRR and LBGi has been validated in previous studies, no study has investigated the relationship between ADRR, LBGi, or any other SMBG-based metric routinely available in the field with epinephrine counterregulation measured during hypoglycemia induced in hospital conditions. Here we report a combined field plus hospital study that investigated the relationship of glucose variability and risk of hypoglycemia estimated from routine SMBG data with laboratory parameters of insulin sensitivity and counterregulatory response in type 1 diabetes.

Subjects and Methods

Subjects

This investigation was approved by the University of Virginia Institutional Review Board, and all subjects gave informed consent. Forty-one subjects (23 men, 18 women) with type 1 diabetes were first recruited for a field study involving SMBG-based feedback and then continued with inpatient assessment of insulin sensitivity and physiologic and symptom responses to hypoglycemia. The recruitment included outpatients at University of Virginia clinics, former research subjects, and local advertising. All subjects were 18 years of age or older and had type 1 diabetes defined by American Diabetes Association criteria or judgment of the study endocrinologist after review of the clinical history and any available medical records. Because the major goal of the field study was the investigation of hypoglycemia, we preferentially recruited patients with a history of severe or moderate hypoglycemia episodes in the preceding 12 months. Therefore, during the screening process, subjects were asked about the occurrence of severe and moderate hypoglycemic episodes over the past year. Exclusion criteria for the field study included current alcohol or drug abuse, severe depression or psychosis, significant mental impairment, inability to use a glucometer, and pregnancy. Additional exclusion criteria during the inpatient admission included use of oral steroids, anemia (hematocrit <36% for women <38% for men), symptomatic heart disease (e.g., history of myocardial infarction, history of coronary bypass or stenting procedure,

angina, episode of chest pain of cardiac etiology with documented electrocardiogram changes, positive stress test, or catheterization with coronary blockages >50%), right-to-left, bi-directional, or transient right-to-left cardiac shunt, history of congestive heart failure, ischemic heart disease, severe pulmonary disease, allergy to perflutern (Definity®, Lantheus Medical Imaging, Inc., North Billerica, MA), known pulmonary hypertension, and history of an ischemic cerebrovascular event. The inpatient admissions occurred after at least 1 month of baseline SMBG monitoring. Thirty-four subjects completed the entire study procedure (14 women and 20 men), three of whom did not have adequate epinephrine data (see below). Thus, the assessment of insulin sensitivity below is based on 34 subjects, while the assessment of hypoglycemia counterregulation is based on 31 subjects.

SMBG data

During the field study, all patients were given OneTouch® Ultrasmart® glucometers (LifeScan, Milpitas, CA) and test strips sufficient for six SMBG readings/day and were instructed on their proper use for collecting routine SMBG data. To avoid transcription errors, the SMBG data were directly downloaded from each patient's glucometer using the OneTouch diabetes management software. While the time of baseline self-monitoring before a General Clinical Research Center visit can be scheduled varied across the subjects, all computations of the SMBG-based metrics used for this study were based on 28 days of SMBG as described below. The average number of SMBG readings/day was 4.84 (range, 3-7).

Clamp description

All patients discontinued long-acting insulin 60 h before the clamp and intermediate-acting insulin 36 h before the clamp. On the day prior to the clamp, only short- or rapid-acting insulin was used. All subjects were admitted to the University of Virginia General Clinical Research Center on the evening prior to the study. At 21:30 h, an overnight insulin infusion consisting of regular insulin (Novolin® R, Novo Nordisk, Copenhagen, Denmark) in 0.9% NaCl at a concentration of 1:1 was titrated to control the subjects' BG overnight between 100 and 150 mg/dL by blood sampling for plasma glucose via the YSI analyzer (YSI Life Sciences, Yellow Springs, OH) every 30 min and adjusting the rate of insulin infusion as needed. At the beginning of the clamp (time 0), the overnight insulin was replaced by an insulin infusion (concentration 1:10) via a Harvard pump (Harvard Apparatus, Holliston, MA) given as a 20 mU/kg priming over a 10-min period, followed by a constant rate delivery of 1 mU/kg/min until the end of the clamp. Blood was sampled for plasma glucose at intervals of at most 5 min, and glucose was clamped at basal levels for the euglycemic control period of 150 min via a variable-rate infusion of 20% dextrose using the equations of DeFronzo et al.¹⁴ Immediately after, the glucose concentration was lowered at a rate of 1 mg/dL/min to a minimum of 50 mg/dL, where it was held constant for 30 min. Finally, the glucose concentration was increased at a rate of 1 mg/dL/min to 90 mg/dL, where it was held for an additional 30 min. Blood was sampled for epinephrine during euglycemia, hypoglycemia, and recovery at times of 140, 175, 185, 195, 205, 215, 225, 235, 245, 255, 265, 275, and 285 min from the beginning of the clamp. The samples

were centrifuged and stored in a -80°F freezer until analyzed with high-performance liquid chromatography.

Indices based on SMBG data

The ADRR and LBGI are based on a previously reported symmetrization of the BG measurement scale.³ The LBGI, a metric introduced more than 10 years ago, is specifically designed to calculate the risk for hypoglycemia as reflected by SMBG data.¹⁵ The LBGI is a non-negative quantity that increases when the number and/or extent of low BG readings increases. In studies, the LBGI typically accounted for 40–55% of the variance of future significant hypoglycemia in the subsequent 3–6 months.^{15–17} The LBGI has established risk categories: Low Risk, $\text{LBGI} < 2.5$; Moderate Risk, $2.5 \leq \text{LBGI} < 5$; and High Risk, $\text{LBGI} \geq 5$, indicating an over 10-fold increase in future severe hypoglycemia from the lowest to the highest risk category.¹⁵ The ADRR has been shown superior to traditional glucose variability measures in terms of risk assessment and prediction of extreme glycemic excursions.⁴ Specifically, it has been demonstrated that classification of risk for hypoglycemia based on ADRR categories (Low Risk, $\text{ADRR} < 20$; Moderate Risk, $20 \leq \text{ADRR} < 40$; and High Risk, $\text{ADRR} \geq 40$) resulted in a severalfold increase in risk for hypoglycemia and hyperglycemia from its lowest to its highest risk category.⁴ The calculation of the ADRR is rather flexible: it only requires having >14 days within a month with three or more measurements per day.⁴ In addition to ADRR and LBGI we computed the following glycemic variability indices: Glycemic Lability Index (GLI),¹⁸ Mean Amplitude of Glycemic Excursions (MAGE),¹⁹ M-value,²⁰ sample SD, and the Variability Index (VI).²¹ All of the above measures are well known, possibly with the exception of the M-value, which is one of the first metrics of glycemic control: the M-value is a measure based on a weighted average of the mean and the glycemic range and, like the ADRR and LBGI, involves a logarithmic transformation of the data.

Clamp metrics

We calculated insulin sensitivity using the equations of DeFronzo et al.¹⁴ along with the recommendations of Roden²² (Chapter 4) as follows: First, we calculated glucose consumption (M) for each of the four 15-min intervals from the 60th to the 120th min of the clamp procedure. (M) was estimated as the glucose infusion rate (INF) minus the space correction (SC) calculated as change in plasma glucose concentration (in mg/dL) multiplied by effective volume divided by 15 and by the subject weight. Note that in our case we did not include a urinary loss of glucose correction (UC) because we performed a euglycemic clamp (Roden,²² Chapter 4). Using the value of 0.19 L/kg for the effective volume, the expression for the space correction reduces to the product of the change in plasma glucose concentration and 0.127. Then the glucose consumption (M) for the interval 60–120 min was averaged from the values estimated for the 15-min intervals. Finally, we calculated the insulin concentration (I) as the weighted average of all the total insulin measurements made in the interval from 60 to 120 min, and insulin sensitivity (SI) was estimated as the ratio (M) over (I). The maximum epinephrine response during hypoglycemia was the maximum concentration of all epinephrine measurements taken at plasma glucose level lower than 70 mg/dL.

Database cleaning

We computed all SMBG measures using 28 days of data with three or more readings/day that were closest to the day of the clamp procedure, with all measurements made within 60 days of the clamp procedure. This choice is valid for the risk-based measures (ADRR, LBGI); moreover, the fixed number of days allows for avoiding potential confounds that might result from using different numbers of measurements for different subjects. The SMBG data of two subjects did not meet these criteria. Furthermore, three clamp procedures were cancelled because of lack of adequate venous access, and two clamp data sets were discarded following the recommendations of Roden²² (Chapter 4) because in at least one of the 15-min intervals used to calculate insulin sensitivity, plasma glucose levels changed by more than 10 mg/dL. This data cleaning left 34 complete data sets for the analysis of insulin sensitivity and 31 data sets for the analysis of epinephrine counterregulation because one of the subjects did not go into hypoglycemia ($\text{BG} < 70 \text{ mg/dL}$) during the clamp and two other subjects had no adequate laboratory values for their epinephrine samples taken during hypoglycemia.

The characteristics of the 34 subjects who had complete data were as follows: 14 women and 20 men; age, 37 ± 2.1 (range, 18–58) years; weight, 78 ± 2.2 (range, 48–110) kg; HbA1c, $7.6 \pm 0.21\%$ (range, 5.5–11%). The characteristics of the 31 subjects (12 women and 19 men) who had adequate epinephrine data as well were virtually identical: age, 37 ± 2.1 (range, 18–58) years; weight, 79 ± 2.2 (range, 61–110) kg; HbA1c, $7.6 \pm 0.22\%$ (range, 5.5–11%).

Statistics and power analysis

All statistics were calculated using the open source statistical package R.²³ For all tests statistical significance was set at 0.05. Spearman partial correlations adjusted for age, duration of diabetes, body mass index, gender, and HbA1c were used to assess all relationships between the field indices of glucose variability and the physiological characteristics of diabetes. Differences between means were assessed by Wilcoxon signed rank test.²⁴ The power analysis for this study was based on preliminary data,²⁵ and the study was powered to detect medium-size correlation (0.4–0.5) with power greater than 80%, which resulted in sample size of $n = 21$ to $n = 34$ subjects.²⁶ Thus, with the achieved sample size, this study is powered to detect correlations of 0.4 and above. For studies involving hyperinsulinemic clamp, $n = 34$ is a large number of subjects. For example, the classic study of DeFronzo et al.,¹⁴ which introduced the glucose clamp technique, had 11 participants.

Results

None of the patient characteristics—age, gender, body mass index, HbA1c, or duration of diabetes—correlated with insulin sensitivity or with epinephrine response during induced hypoglycemia. The largest observed correlation was between HbA1c and maximum epinephrine response ($\rho = 0.24$, P non-significant). Nevertheless, in all subsequent analyses we used these variables as covariates, which helped isolate the strengths of the direct relationships between glucose variability/risk for hypoglycemia and insulin sensitivity and epinephrine counterregulation. Tables 1 and 2 present the

TABLE 1. PARTIAL CORRELATION (WITH AGE, BODY MASS INDEX, GENDER, AND GLYCOSYLATED HEMOGLOBIN AS COVARIATES) OF INSULIN SENSITIVITY WITH MEASURES OF GLUCOSE VARIABILITY AND RISK FOR HYPOGLYCEMIA

Glucose variability/ hypoglycemia risk measure	Partial correlation	P value
Average Daily Risk Range (ADRR)*	0.50	0.002
Glycemic Lability Index (GLI)*	0.48	0.003
Low BG Index (LBGI)*	0.26	0.157
Mean Amplitude of Glycemic Excursions (MAGE)	0.18	0.335
M-Value	0.35	0.050
SD	0.38	0.029
Variability Index (VI)	0.29	0.107

The most significant values are shown in bold type.

*ADRR, GLI, and LBGI can be interpreted as glucose variability measures designed to be particularly sensitive to hypoglycemic excursions.

Spearman partial correlations of insulin sensitivity (Table 1) and maximum epinephrine observed during hypoglycemia (Table 2) with several metrics of glucose variability and risk for hypoglycemia.

Glucose variability and insulin sensitivity

Table 1 suggests that glucose variability measured in the field from SMBG data correlates with insulin sensitivity measured in hospital conditions through euglycemic hyperinsulinemic clamp. The (generic) SD of SMBG data was positively correlated with insulin sensitivity ($\rho = 0.38$, $P = 0.029$), but higher correlations were achieved by more sophisticated metrics of glucose variability, such as the ADRR and the GLI, which were specifically designed to measure glucose variability in diabetes ($\rho = 0.50$ and $\rho = 0.48$, respectively; both P levels below 0.005).

Traditional measures of variability, such as MAGE and VI, were not correlated with insulin sensitivity, which can be explained by the fact that by design both of these metrics are more prominently influenced by the high end of the glucose scale than by the low end of the scale (this property is purely numerical and is a function of the definition of these metrics).

Risk for hypoglycemia and counterregulation

Data in Table 2 suggest that glucose variability is associated with the epinephrine response during induced hypoglycemia, but contrary to the association with insulin sensitivity, this correlation here is negative. Again, the generic SD is marginally correlated with epinephrine response ($\rho = -0.36$, $P = 0.052$), but, as in the previous paragraph, metrics that are specifically designed to assess risk for hypoglycemia in diabetes resulted in better pronounced relationships. Specifically, the LBGI, which is designed to be sensitive to hypoglycemia alone, exhibited the highest correlation coefficient ($\rho = 0.46$, $P = 0.009$), followed by the ADRR. As expected, MAGE and VI had correlations close to zero because of their exclusive sensitivity to hyperglycemic excursions alone. Stratifying the study population into Low versus Moderate-High Risk for

TABLE 2. PARTIAL CORRELATION (WITH BODY MASS INDEX, GENDER, GLYCOSYLATED HEMOGLOBIN, AND YEARS OF DISEASE AS COVARIATES) OF MAXIMUM EPINEPHRINE RESPONSE DURING INDUCED HYPOGLYCEMIA WITH MEASURES OF GLUCOSE VARIABILITY AND RISK FOR HYPOGLYCEMIA

Glucose variability/ hypoglycemia risk measure	Partial correlation	P value
Average Daily Risk Range (ADRR)	-0.4	0.029
Glycemic Lability Index (GLI)	-0.12	0.559
Low BG Index (LBGI)	-0.46	0.009
Mean Amplitude of Glycemic Excursions (MAGE)	0.03	0.884
M-Value	-0.29	0.124
SD	-0.36	0.052
Variability Index (VI)	-0.12	0.529

The most significant values are shown in bold type.

hypoglycemia along the categories of the LBGI (i.e., LBGI < 2.5 vs. LBGI ≥ 2.5) or into Low-Moderate versus High Risk along the categories of the ADRR (ADRR < 40 vs. ADRR ≥ 40) resulted in a significantly different epinephrine response. Figure 1A presents a mean epinephrine response of 495 pg/mL in the LBGI Low-Risk group versus 217 pg/mL in subjects classified at Moderate-High Risk for hypoglycemia by the LBGI ($P = 0.003$). Similarly, compared to high-risk subjects, subjects at low to moderate risk according to the ADRR had a higher epinephrine response (417 pg/mL vs. 167 pg/mL, $P = 0.026$) (Fig. 1B).

Finally, an exploratory factor analysis revealed that a single factor maybe underlying both insulin sensitivity and epinephrine response during hypoglycemia (factor loadings of 0.71 and -0.71, respectively). This factor explained approximately 74% of the variance of these two seemingly disparate physiological parameters and had a Spearman correlation of $\rho = 0.41$ with the LBGI ($P = 0.023$).

Discussion

Our results support the hypothesis that glucose variability as quantified by several SMBG-based metrics (ADRR, GLI, SD) correlates positively with insulin sensitivity as quantified by a hyperinsulinemic euglycemic clamp procedure, irrespective of HbA1c levels. One explanation of this result is that patients with high insulin sensitivity have more difficulties controlling their diabetes because small errors in insulin dosing would result in larger errors in treatment. Thus high insulin sensitivity could cause increased glucose variability. Another possible physiological explanation is that glucose variability affects insulin sensitivity through hypoglycemia. In particular, Inouye et al.²⁷ demonstrated that recurrent hypoglycemia in rats with diabetes increases glucose consumption. Combining the assumption that these researchers' result would hold for type 1 diabetes patients with the well-established connection between hypoglycemia and glucose variability²⁸⁻³⁰ provides a probable explanation for our findings.

On the other hand, it has been well established that episodes of antecedent hypoglycemia could cause defective epinephrine counterregulation.⁵⁻⁷ This relationship explains

FIG. 1. (A) Maximum epinephrine (MaxEpi) response during hypoglycemia across the Low versus Moderate-High Risk categories defined by the Low Blood Glucose Index (LBGI). (B) MaxEpi response during hypoglycemia across the Low-Moderate versus High-Risk categories defined by the Average Daily Risk Range.

our findings of negative correlation between LBGI and maximum epinephrine concentration during hypoglycemia. In particular, because high LBGI indicates increased frequency and extent of mild hypoglycemic excursions, the mechanism of repeated hypoglycemia causing defective epinephrine counterregulation is well manifested by these data. Specifically, here we can speculate that the negative correlation of the LBGI and the ADRR with maximum epinephrine response during hypoglycemia reflects the causal effect of repeated hypoglycemia on subsequent counterregulatory deficiency. In general, correlation does not imply cause, but in this particular case assuming causality is logical. Nevertheless, the process of repeated mild hypoglycemia and counterregulatory depletion is recurrent, a “vicious cycle”³¹ that sometimes could be interrupted by meticulous avoidance of hypoglycemia.^{11,12} Thus, having a reflection of impaired counterregulatory response and increased risk for hypoglycemia that is readily available in the field from routine SMBG data could provide valuable information to patients and their physicians.

In terms of metrics, this study shows that not all measures of variability are created equal. It becomes apparent that glucose variability is a multifaceted property and that different measures capture different aspects of its manifestation. For example, traditional metrics such as MAGE and even SD tend to be more sensitive to hyperglycemic excursions and tend to ignore hypoglycemia. The reasons for that are purely numerical and have been discussed in the past:^{3,16} the glucose measurement scale is inherently asymmetric, the hypoglycemic range is numerically much narrower than the hyperglycemic range, and the risk for hypoglycemia increases much more rapidly with falling BG than would the risk for hyperglycemia with glucose increasing by the same increments. This asymmetry explains why certain metrics, such as the ADRR and the LBGI, which are based on a symmetrizing transformation of the BG scale,³ are more sensitive to the physiological manifestations of insulin sensitivity and impaired hypoglycemia counterregulation. Therefore, it is important to select an appropriate variability metric depending

on the task in hand: if hyperglycemia and postprandial glucose excursions are of concern, MAGE would be a measure of choice; if hypoglycemia is the primary target for investigation, LBGI is arguably the best choice. ADRR was designed to optimally balance both hypo- and hyperglycemic excursions and to suppress (numerically) glucose fluctuations with the safe target range; thus, the ADRR would be preferable when overall glycemic variability and extreme glucose excursions are investigated.⁴

Finally, our findings support the hypothesis of existence of a less known relationship between recurrent hypoglycemia and high insulin sensitivity. In addition to our main results, we found a negative correlation between insulin sensitivity and maximum epinephrine concentration during hypoglycemia ($\rho = -0.37$, $P = 0.04$) and established that these two variables could be represented by a single underlying factor explaining 74% of their variance. However, these data do not allow further investigation of this phenomenon and cannot render a physiological explanation. One possibility would be that hepatic glucose production could be underlying both the hepatic (as opposed to the peripheral) component of insulin sensitivity and the counterregulatory response to hypoglycemia, but this cannot be established by these data. Other limitations of this study include the nonphysiologic assessment of insulin sensitivity (e.g., we used the clamp instead of a more physiologic meal test³²) and the lack of field data for the regular insulin dose of the participants, which precluded the evaluation of certain aspects of the patient treatment.

Possible directions for future research include building a detailed network model that would explain mechanistically the observed relationships and would allow for dynamical evaluation of changes in insulin sensitivity and/or counterregulatory ability from SMBG and continuous glucose monitoring data. Such a model could assist achieving a stricter glycemic control by providing real-time suggestions for more precise insulin dosing and warnings about increased risk for hypoglycemia. Of particular relevance would be the implementation of such technology into the closed-loop control systems of the near future.

Acknowledgments

This work was supported by grants RO1 DK 51562 and RO1 DK 085623 from the National Institutes of Health, by the General Clinical Research Center at the University of Virginia, and by material support from LifeScan Inc., Milpitas, CA. The authors thank Pamela Mendosa, R.N. for her coordination of this study and Jeff Hawley for his assistance with the preparation of this manuscript.

Author Disclosure Statement

B.K. has received grant support and patent royalties from Lifescan, Inc., Milpitas, CA, a manufacturer of self-monitoring devices. A.N.P. and S.M.A. declare no competing interests exist.

References

- Hirsch IB: Blood glucose monitoring technology: translating data into practice. *Endocr Pract* 2004;10:67–76.
- Bragd J, Adamson U, Bäcklund LB, Lins PE, Moberg E, Oskarsson P: Can glycaemic variability, as calculated from blood glucose self-monitoring, predict the development of complications in type 1 diabetes over a decade? *Diabetes Metab* 2008;34:612–616.
- Kovatchev BP, Cox DJ, Gonder-Frederick LA, Clarke W: Symmetrization of the blood glucose measurement scale and its applications. *Diabetes Care* 1997;20:1655–1658.
- Kovatchev BP, Otto E, Cox D, Gonder-Frederick L, Clarke W: Evaluation of a new measure of blood glucose variability in diabetes. *Diabetes Care* 2006;29:2433–2438.
- Cryer PE: The barrier of hypoglycemia in diabetes. *Diabetes* 2008;57:3169–3176.
- Bolli G, de Feo P, Compagnucci P, Cartechini MG, Angeletti G, Santeusano F, Brunetti P, Gerich HE: Abnormal glucose counterregulation in insulin-dependent diabetes mellitus. Interaction of anti-insulin antibodies and impaired glucagon and epinephrine secretion. *Diabetes* 1983;32:134–141.
- Dagogo-Jack SE, Craft S, Cryer PE: Hypoglycemia-associated autonomic failure in insulin-dependent diabetes mellitus. Recent antecedent hypoglycemia reduces autonomic responses to, symptoms of, and defense against subsequent hypoglycemia. *J Clin Invest* 1993;91:819–828.
- Jones TW, Porter P, Sherwin RS, Davis EA, O'Leary P, Frazer F, Byrne G, Stick S, Tamborlane W: Decreased epinephrine responses to hypoglycemia during sleep. *N Engl J Med* 1998;338:1657–1662.
- Diabetes Research in Children Network (DirecNet) Study Group: Impaired overnight counterregulatory hormone responses to spontaneous hypoglycemia in children with type 1 diabetes. *Pediatr Diabetes* 2007;8:199–205.
- Graveling AJ, Warren RE, Frier BM: Blunted counterregulatory hormone responses to hypoglycemia in young children and adolescents with well-controlled type 1 diabetes: response to the Diabetes Research in Children Network (DirecNet) Study Group. *Diabetes Care* 2010;33:e67; author reply e68.
- Fanelli CG, Epifano L, Rambotti AM, Pampanelli S, Di Vincenzo A, Modarelli F, Lepore M, Annibale B, Ciofetta M, Bottini P: Meticulous prevention of hypoglycemia normalizes the glycemic thresholds and magnitude of most of neuroendocrine responses to, symptoms of, and cognitive function during hypoglycemia in intensively treated patients with short-term IDDM. *Diabetes* 1993;42:1683–1689.
- Cranston I, Lomas J, Maran A, Macdonald I, Amiel SA: Restoration of hypoglycemia awareness in patients with long-duration insulin-dependent patients. *Lancet* 1994;344:283–287.
- Bergman RN, Ider YZ, Bowden CR, Cobelli C: Quantitative estimation of insulin sensitivity. *Am J Physiol* 1979;236:E667–E677.
- DeFronzo RA, Tobin JD, Andres R: Glucose clamp technique: a method for quantifying insulin secretion and resistance. *Am J Physiol Gastrointest Liver Physiol* 1979;237:G214–G223.
- 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* 1998;21:1870–1875.
- 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 data. *Diabetes Technol Ther* 2003;5:817–828.
- Cox DJ, Gonder-Frederick LA, Ritterband L, Clarke WL, Kovatchev BP: Prediction of severe hypoglycemia. *Diabetes Care* 2007;30:1370–1373.
- Ryan EA, Shandro T, Green K, Paty BW, Senior PA, Bigam D, Shapiro AM, Vantyghem MC: Assessment of the severity of hypoglycemia and glycemic lability in type 1 diabetic subjects undergoing islet transplantation. *Diabetes* 2004;53:955–962.
- Service FJ, Molnar GD, Rosevear JW, Ackerman E, Gatewood LC, Taylor WT: Mean amplitude of glycemic excursions, a measure of diabetic instability. *Diabetes* 1970;19:644–655.
- Schlichtkrull J, Munck O, Jersild M: The M-Value, an index of blood-sugar control in diabetics. *Acta Med Scand* 1965;177:95–102.
- SMandrekhar SJ, HNagaraja HN, Berntson GG: Statistical modelling of the differences between successive R-R intervals. *Statistics Med* 2005;24:437–451.
- Roden M: *Clinical Diabetes Research: Methods and Techniques*. New York: Wiley, 2007.
- R Development Core Team: *R: A Language and Environment for Statistical Computing*. Vienna: R Foundation for Statistical Computing, 2009.
- Sprent P, Smeeton NC: *Applied Nonparametric Statistical Methods*. Boca Raton, FL: CRC Press, 2000.
- Kovatchev BP, Anderson SM, Otto E: Field glucose variability index is related to laboratory measures of insulin sensitivity and hypoglycemia counterregulation [abstract]. *Diabetologia* 2006;49(Suppl 1):A855.
- Faul F, Erdfelder E, Lang A-G, Buchner A: G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods* 2007;39:175–191.
- Inouye K, Shum K, Chan O, Mathoo J, Matthews SG, Mladen Vranic M: Effects of recurrent hyperinsulinemia with and without hypoglycemia on counterregulation in diabetic rats. *Am J Physiol Endocrinol Metab* 2002;282:E1369–E1379.
- Kovatchev BP, DCox DJ, Farhy LS, Straume M, Gonder-Frederick L, 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* 2000;85:4287–4292.
29. Jeha GS, Karaviti LP, Anderson B, Smith EOB, Donaldson S, McGirk TS, Haymond MW: Insulin pump therapy in preschool children with type 1 diabetes mellitus improves glycemic control and decreases glucose excursions and the risk of hypoglycemia. *Diabetes Technol Ther* 2005;7: 876–884.
30. Kudva YC, Basu A, Jenkins GD, Pons GM, Vogelsang DA, Rizza RA, Smith SA, Isley WL: Glycemic variation and hypoglycemia in patients with well-controlled type 1 diabetes on a multiple daily insulin injection program with use of glargine and ultralente as basal insulin. *Endocr Pract* 2007;13:244–250.
31. Cryer PE: Iatrogenic hypoglycemia as a cause of hypoglycemia-associated autonomic failure in IDDM: a vicious cycle. *Diabetes* 1992;41:255–260.
32. Caumo A, Bergman RN, Cobelli C: Insulin sensitivity from meal tolerance tests in normal subjects: a minimal model index. *J Clin Endocrinol Metab* 2000;85:4396–4402.

Address correspondence to:

Boris Kovatchev, Ph.D.

Department of Psychiatry and Neurobehavioral Sciences

University of Virginia Health System

P.O. Box 400888

Charlottesville, VA 22904

E-mail: boris@virginia.edu