Evaluation of a New Measure of Blood Glucose Variability in Diabetes

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OBJECTIVE — Recent studies show the importance of controlling blood glucose variability in relationship to both reducing hypoglycemia and attenuating the risk for cardiovascular and behavioral complications due to hyperglycemia. It is therefore important to design variability measures that are equally predictive of low and high blood glucose excursions.

RESEARCH DESIGN AND METHODS — We introduce the average daily risk range (ADRR), a variability measure computed from routine self-monitored blood glucose (SMBG) data. The ADRR was constructed using a development dataset for 39 and 31 adults with type 1 and type 2 diabetes, respectively. The formula was then fixed, and the ADRR was compared against other variability measures using an independent validation dataset containing ~4 months of SMBG for 254 and 81 adults with type 1 and type 2 diabetes.

RESULTS — From the 1st month of validation SMBG data, we computed the ADRR, blood glucose SD and coefficient of variation, daily blood glucose range and interquartile range, mean amplitude of glycemic excursion, M-value, and lability index. Then all measures were tested as predictors of low blood glucose (<2.2 mmol/l; <3.9 mmol/l) and high (>10 mmol/l; >22.2 mmol/l) events in the subsequent 3 months. The ADRR was the best predictor of both hypoglycemia and hyperglycemia, with a 6-fold increase in the likelihood of hypoglycemia and 3.5-fold increase in the likelihood of hyperglycemia across its risk categories.

CONCLUSIONS — In a large SMBG database, the ADRR showed strong association with subsequent out-of-control glucose readings. Compared with other variability measures, the ADRR demonstrated a superior balance of sensitivity to predicting both hypoglycemia and hyperglycemia. This prediction was independent from type of diabetes.

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HbA_{1c} (A1C) is the standard measure of average glycemic control (1) predicting diabetes complications in type 1 and type 2 diabetes (2,3). However, in addition to establishing A1C, the Diabetes Control and Complications Trial concluded that "A1C is not the most complete expression of the degree of glycemia. Other features of diabetic glucose control, which are not reflected by A1C, may add to or modify the risk of complications. For example, the risk of complications may be more highly dependent on the extent of postprandial glycemic excursions" (4). Consequently, contemporary studies increasingly investigate blood glucose fluctuations, specifically hypoglycemia and postprandial glycemic elevation.

Hypoglycemia is common in type 1 diabetes (5) and becomes more prevalent in type 2 diabetes with treatment intensification (6). State-of-the-art therapies are still imperfect and may trigger acute blood glucose lowering, potentially leading to cognitive dysfunction, stupor, or death. Consequently, hypoglycemia has been identified as the primary barrier to optimal diabetes management (7,8). However, A1C is a poor predictor of hypoglycemic episodes, accounting for ~8% of future severe hypoglycemia (5). In contrast, specific variability-based measures accounted for 40–50% of the variance of future significant hypoglycemia (9–11). Indeed, the recent American Diabetes Association consensus statement on hypoglycemia concluded that "history of severe hypoglycemia and lower A1C levels have limited ability to predict additional episodes . . . [while] >50% of hypoglycemia can be predicted based on risk [variability] analysis of self-monitored plasma glucose data over time" (12).

At the high end of the blood glucose scale, factors such as insulin resistance, inadequate available insulin, delayed insulin action, or abnormal glucagon secretion contribute to higher and prolonged postprandial glycemic elevation (13,14). A number of studies found that, in addition to causing microvascular complications, hyperglycemia is an independent contributor to cardiovascular disease and increased mortality, especially in type 2 diabetes (15–18). It is hypothesized that this is due to oxidative stress, which may promote macrovascular complications (19–21). Experiments continue to support the notion that hyperglycemia is a major determinant of atherosclerosis progression (16,22–24).

Therefore, the complex interplay between physiology and behavior in diabetes results in significant blood glucose fluctuations that have a deleterious impact on the incidence of acute and chronic complications. This dynamic is reflected not only, and maybe not primarily, by average glycemia, but the major display of blood glucose fluctuations is also their variability across low and high blood glucose values. Thus, we can conclude that the ability of patients to tightly control their glycemic variation may become a paramount task of diabetes control. In fact, a recent review concluded that "glucose variability, considered in combination with A1C, maybe a more reliable indicator of blood glucose control and the risk for long-term complications than mean A1C alone" (25). Therefore, it becomes essential for clinical practice to use the best methods available for the evaluation of glucose variability to provide the most relevant feedback to improve glyce-

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Abbreviations: ADRR, average daily risk range; HBGI, high blood glucose index; LBGI, low blood glucose index; MAGE, mean amplitude of glucose excursions; SMBG, self-monitored blood glucose.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.
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mic control. Ultimately, the evaluation of blood glucose variability should be predictive of both hypoglycemic and hyperglycemic blood glucose excursions, thereby accounting for both ends of extreme blood glucose fluctuation.

However, most available measures, including average blood glucose, SD, interquartile range, and others, are primarily dependent on hyperglycemic blood glucose excursions and are generally insensitive to hypoglycemia. This is due to the inherent asymmetry of the blood glucose scale, which can be numerically corrected as we have shown in the past (26). We now describe the development and the testing of a new diabetes-specific measure of variability, the average daily risk range (ADRR), which is designed to be equally sensitive to hypoglycemia and hyperglycemia and is easily computed from routine self-monitored blood glucose (SMBG) readings.

RESEARCH DESIGN AND METHODS

— This investigation used de-identified archival SMBG data from studies conducted at the University of Virginia and at LifeScan over the past 4 years. There were two independent datasets: a development dataset that was used to create a formula of the ADRR and a larger validation dataset that allowed the independent comparison of the ability of the ADRR to predict future extreme blood glucose episodes versus other variability measures.

The development dataset contained SMBG records for $n = 70$ adults, 39 of whom had type 1 diabetes and 31 had type 2 diabetes. The demographic characteristics of these type 1/type 2 diabetic subjects were as follows (average ± SD): age 38.8 ± 11.0/50.2 ± 8.2 years; percent male 52/38%; BMI 26.0 ± 4.7/35.9 ± 8.9 kg/m^2; duration of diabetes 19.8 ± 10.8/13.1 ± 10.2 years; baseline A1C 7.7 ± 1.2/8.2 ± 1.6%); and number of SMBG readings/day 4.2 ± 1.0/3.7 ± 0.8. The demographics in the validation dataset ($n = 254$ type 1 diabetes/$n = 81$ type 2 diabetes) were as follows: age 32.0 ± 17.4/53.2 ± 8.9 years; percent male 48/44%; BMI 23.8 ± 4.8/34.3 ± 9.3 kg/m^2; duration of diabetes 15.8 ± 12.3/11.6 ± 7.4 years; baseline A1C 8.1 ± 1.3/8.5 ± 1.5%; and number of SMBG readings per day 3.8 ± 2.1/3.4 ± 1.5. Each subject had 4 months of SMBG readings, which were split into month 1 used to compute all variability measures and months 2–4 used to test their predictive utility.

Using the development data, we have designed the ADRR to be equally sensitive to hypoglycemic and hyperglycemic blood glucose deviations and optimized its parameters. The optimization criterion was the ability of the measure to predict equally well future extreme hypoglycemia (defined as blood glucose <2.2 mmol/l) and extreme hyperglycemia (blood glucose >22.2 mmol/l). The cutoffs, 2.2 mmol/l (40 mg/dl) and 22.2 mmol/l (400 mg/dl), were selected to reflect clinical perceptions of extreme glycemia (e.g., 40–400 variability). Prediction involving moderate hypoglycemic (blood glucose <3.9 mmol/l) and hyperglycemic (blood glucose >10 mmol/l) events was considered as well.

The ADRR is computed using the formulas below from 2–4 weeks of SMBG data with a frequency of ≥3 SMBG readings/day. It is important to note that the computation does not require consecutive days with ≥3 readings/day; it is sufficient to have 14 days with ≥3 readings/day over 1 month. A formal description of the ADRR algorithm follows:

Let $x_1^i, x_2^i, \ldots x_n^i$ be a series of n^i SMBG readings taken on day i, $i = 1,2,\ldots, M$. It is required that $14 < M < 30$ and $n^1, n^2, \ldots, n^M \geq 3$. In other words, it is required the $M > 14$ days within a month to have at least 3 SMBG readings/day.

Further, because of the asymmetric nature of the blood glucose scale, calculation of the ADRR is based on our previously introduced data transformation that normalizes the blood glucose scale (26). Each SMBG reading is first transformed using the formula $f(\text{BG}) = 1.509.\{[\ln(\text{BG} \times 18)]^{1.084} - 5.381\}$ for blood glucose (BG) measured in millimoles per liter (the multiplication by 18 in the logarithm is omitted if blood glucose is measured in milligrams per deciliter). Then we convert the blood glucose readings into risk values using the formula $r(\text{BG}) = f(\text{BG})$ (2) and taking separately the left and right branch of the resulting parabola as indicators of risk for hypoglycemia and hyperglycemia, respectively:

$\text{rl}(\text{BG}) = r(\text{BG})$ if $f(\text{BG}) < 0$ and 0 otherwise (left branch);

$\text{rh}(\text{BG}) = r(\text{BG})$ if $f(\text{BG}) > 0$ and 0 otherwise (right branch).

Finally, the ADRR is computed as the average of the risk range per day using the formula

$$\text{ADRR} = \frac{1}{M}\sum_{i=1}^{M}[\text{LR}^i + \text{HR}^i]$$

where $\text{LR}^i = \max[\text{rl}(x_1^i), \ldots, \text{rl}(x_n^i)]$ and $\text{HR}^i = \max[\text{rh}(x_1^i), \ldots, \text{rh}(x_n^i)]$ for day i; $i = 1,2,\ldots M$.

In summary, the computation of the ADRR is equivalent to computing average daily blood glucose range over 30 days, but the blood glucose data are first normalized and converted into their corresponding risk values. Thus, we have a two-cycle data aggregation (day-month) preceded by a normalizing transformation of logarithmic type (26). The complexity of calculation is therefore similar to that of *M*-value (27) (requiring transformation) and the lability index (28) (requiring two-cycle data aggregation). Thus, the ADRR can be easily implemented in a spreadsheet or software. Based on the distribution of the ADRR in the development data, its values were stratified into three categories: low risk, ADRR <20; moderate risk, ADRR 20–40; and high risk, ADRR >40. The optimal observation period was 1 month, with a testing frequency of 3–5 readings/day.

The formula for the ADRR, as well as the ADRR risk categories, were then fixed and subsequently confirmed using the validation data to compare the predictive ability of the ADRR versus an extensive list of measures of average glycemia and blood glucose variability, including *1*) baseline A1C; *2*) average blood glucose; *3*) number of hypoglycemic and hyperglycemic readings; *4*) SD of blood glucose; *5*) coefficient of variation (CV) of blood glucose; *6*) average daily blood glucose range (maximum − minimum value of blood glucose per day); *7*) *M*-value (27); *8*) mean amplitude of glucose excursions (MAGE) (29); *9*) interquartile range; and 10) lability index, a measure of hypoglycemia and glycemic lability (28). Our previously introduced low blood glucose index (LBGI) and high blood glucose index (HBGI) (9,10) were tested as well. The LBGI and the HBGI are based on the same normalizing transformation as the ADRR but are specifically designed to be sensitive to hypoglycemia and hyperglycemia, respectively, and to have zero correlation with their opposite ranges of the blood glucose scale.

The analyses confirming the ADRR with the validation data included *1*) computing all measures from the 1st month of SMBG and *2*) correlating these measures with the number of future extreme hypoglycemic, hypoglycemic (blood glucose <3.9 mmol/l), hyperglycemic (blood glucose >10 mmol/l), and extreme hyper-

glycemic events during months 2–4 of SMBG readings. χ^2 tests were used to study the association of the risk categories of the ADRR with future hypoglycemia, euglycemia, and hyperglycemia. Because the other variability measures do not have a specified categorization, this analysis was limited to the ADRR. A general linear model was used to test the relative contribution of type of diabetes and ADRR to future normoglycemia.

RESULTS

Development dataset

The correlations of the optimized ADRR with the number of extreme hypoglycemic and hyperglycemic events over the next 3 months were 0.40 and 0.53, respectively, and the correlations with blood glucose values <3.9 mmol/l and >10 mmol/l were 0.41 and 0.63, respectively (all $P < 0.001$). Although some of the other measures were better related than the ADRR to future hyperglycemia, no other measures were related to future hypoglycemic episodes. For example, the average blood glucose and the SD of blood glucose from month 1 had significant correlations with future hyperglycemia (blood glucose >10 mmol/l): 0.67 and 0.50, respectively ($P < 0.001$). However, these measures had nonsignificant correlations with future hypoglycemia (blood glucose <3.9 mmol/l): −0.19 and 0.28, respectively.

Validation dataset

Figure 1 illustrates the concept of this article with the first 30 days of SMBG data for three subjects who had similar average blood glucose levels: subject A 7.9 mmol/l, subject B 7.8 mmol/l, and subject C 8.0 mmol/l. Nevertheless, subjects A and B were different in terms of their glucose variability: the SD of blood glucose was 3.0 vs. 5.4 mmol/l for subject A vs. B. More dramatic was the difference in these subjects' ADRRs: 13.8 for subject A, classified in the low-risk ADRR category, and 42.0 for subject B, who was classified at high risk. In the subsequent 3 months, subject A recorded zero extreme blood glucose events. In contrast, subject B recorded 10 extreme events (3 extreme hypoglycemia and 7 hyperglycemia). Thus, the difference in future extreme glycemic excursions was entirely due to increased glucose variability.

Subject C had a relatively low SD (3.8 mmol/l), which was ~25% higher than that of subject A. However, subject C had 2.7-fold higher ADRR (36.8) than subject A. Consequently, subject C recorded six extreme hypoglycemic and zero extreme hyperglycemic events over the next 3 months (compared with zero extreme events for subject A). Thus, subjects A and C were different in their risk for hypoglycemia, which was accurately predicted by the ADRR. This illustrates that the SD of blood glucose is mostly related to variability at the high end of the blood glucose scale and is less sensitive to hypoglycemia.

At a group level, Table 1 presents the correlations between all considered measures computed from month 1 data with subsequent extreme hypoglycemia and hyperglycemic events in month 2, months 2–3, and months 2–4. We present a gradual extension of the follow-up period with the intention to examine the degree of decay in the predictive ability of all measures. It is apparent that the ADRR is the only measure that has consistent significant correlations with both future extreme hypoglycemia and hyperglycemia. As expected, most standard and literature measures correlate predominantly with hyperglycemia, with the exception of the lability index, which was designed to reflect hypoglycemic excursions. The lability index, however, does not increase with event severity to the degree to which the ADRR does. By design, the LBGI and the HBGI are specifically predictive of hypoglycemia and hyperglycemia, respectively, and, as expected, these indexes were better predictors in their respective fields than the composite ADRR. However, by design, the LBGI and the HBGI do not correlate with their opposite blood glucose ranges, hyperglycemia and hypoglycemia, respectively, and therefore cannot be used as overall measures of variability. The decay in the correlation of the ADRR with future extreme glycemic events was not significant from 1- to 3-month predictive horizon.

The same analyses were performed to predict low blood glucose readings (blood glucose <3.9 mmol/l) and high blood glucose readings (blood glucose >10.0 mmol/l). In these analyses, the ADRR was also comparable or superior to all other measures tested. Thus, the ADRR is not only predicting those with severe outlier glucose readings but is linearly associated with progressively higher frequency and severity of events. This is elucidated further in Table 2, which shows the distribution of hypoglycemic (blood glucose <3.9 mmol/l), euglycemic (3.9–10 mmol/l), and hyperglycemic (blood glucose >10 mmol/l) events registered during month 2 of the investigation stratified by the categories of the ADRR computed in month 1. In month 1 of the validation dataset, 20% of all subjects were categorized at low risk, 52% were categorized at moderate risk, and 28% were categorized at high risk. It is evident that the percentage of readings within the target range decreases from 71% in the low-risk ADRR category (83.3% in the very-low-risk category, ADRR <10) to 46% in the moderate-risk ADRR category, and further to 35% in the high-risk ADRR category (33.9% in the very-high-risk category, ADRR >50). This association was supported by a highly significant χ^2 test ($P < 0.00001$). Similar χ^2 tests were performed to assess the association between ADRR risk categories in month 1 with the distribution of hypoglycemic, euglycemic, and hyperglycemic readings in months 2–3 and months 2–4, yielding similar P levels (<0.00001).

Finally, using a univariate general linear model, we predicted the percentage of SMBG readings in the euglycemic range (3.9–10 mmol/l) in month 2 of the study using two fixed factors: type of diabetes and risk category determined in month 1. The two factors were sequentially entered in the model; at the first step, type of diabetes alone was a significant predictor of future euglycemia. However, when the ADRR was entered, the type of diabetes was no longer significant. The P levels of the two-factor model were $F = 36.0$, $P < 0.0001$ for the ADRR and $F = 0.25$, $P = 0.61$ for type of diabetes. Thus, given a risk category (i.e., once a certain risk status is achieved), the type of diabetes no longer contributed to the explanation of future normoglycemia.

CONCLUSIONS — This article introduces the ADRR, a new measure for evaluation of blood glucose variability, which is an important dimension of glycemic control in diabetes management (25). The ADRR is computed from routine SMBG data collected over 1 month with a typical (but not required) frequency of 3–5 readings/day. It is important to note that the computation of the ADRR does not require consecutive days with ≥3 readings/day. Resampling experiments have shown that the predictive performance of the ADRR does not decay significantly down to only 14 of 30 days

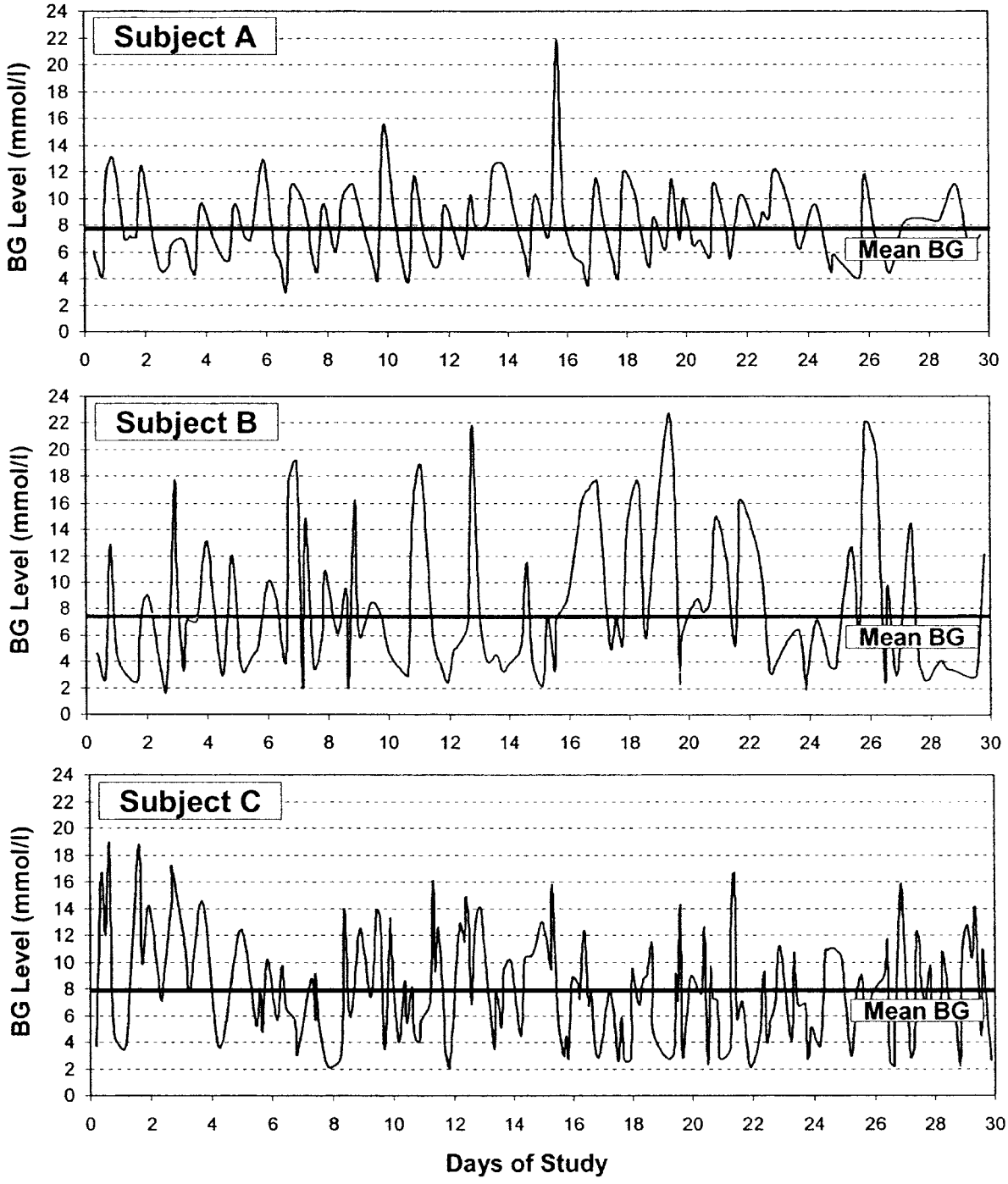

Figure 1— *Illustrative data for three subjects, A, B, and C, who had similar average blood glucose (BG) levels during month 1 of 7.9, 7.8, and 8.0 mmol/l, respectively, represented by thick horizontal lines in each panel. In the subsequent 3 months, subject A recorded 0 extreme blood glucose episodes, whereas subject B recorded 10 such episodes (3 blood glucose <2.2 mmol/l and 7 blood glucose >22.2 mmol/l). This difference was due to higher blood glucose variability in subject B, reflected by 1.8-fold higher SD and 3.1-fold higher ADRR. Subject C had a slightly higher (3.8 vs. 3.0 mmol/l) SD than subject A. Nevertheless, subject C recorded six extreme hypoglycemic episodes in the next 3 months, a difference that was accurately predicted by 2.7-fold higher ADRR. This illustrates that the SD of blood glucose is a measure of variability, which is mostly reflective of hyperglycemia but is less sensitive to risk for hypoglycemia.*

containing ≥3 readings/day. In addition, the dependence of the ADRR on the number of readings per day is marginal and indirect (through the presumably higher likelihood of capturing extreme blood glucoses with more frequent measurement) because only the two extreme-risk readings per day enter the computation.

The new measure combines the LBGI and HBGI based on our previously developed normalization of the blood glucose scale and theory of risk analysis of blood glucose data (9,10). The advantage of such a combination is that a single risk index becomes equally predictive of fu-

Table 1—*Correlations of variability measures with future extreme glycemic events*

	No. of extreme blood glucose values in month of study					
	Month 2		Months 2–3		Months 2–4	
	<2.2 mmol/l	>22.2 mmol/l	<2.2 mmol/l	>22.2 mmol/l	<2.2 mmol/l	>22.2 mmol/l
Measures of average glycemia						
A1C	−0.10	0.58	0.02	0.58	−0.04	0.58
Mean BG	−0.18	0.61	−0.10	0.61	−0.15	0.58
Count of hypoglycemic and hyperglycemic BG events (<3.9 and >10 mmol/l)						
No. BG events	0.43	0.23	0.36	0.16	0.35	0.13
Literature measures of glycemic variability						
SD of BG	0.15	0.65	0.22	0.61	0.15	0.58
CV of BG	0.38	0.26	0.37	0.21	0.33	0.18
M-value	0.17	0.74	0.20	0.72	0.16	0.68
MAGE	0.17	0.64	0.24	0.60	0.17	0.56
IQR	0.14	0.63	0.20	0.59	0.14	0.55
Lability index	0.44	0.39	0.44	0.29	0.37	0.26
Risk measures						
LBGI	0.65	0.01	0.54	−0.04	0.59	−0.06
HBGI	−0.07	0.70	−0.01	0.68	-0.05	0.65
ADRR	0.49	0.56	0.48	0.49	0.44	0.45

At this sample size, correlations >0.4 are significant at $P = 0.001$, which is an appropriate significance level accounting for the multicolinearity of the considered measures. BG, blood glucose; IQR, interquartile range.

ture extreme glucose excursions into hypoglycemia and hyperglycemia, which resolves a major problem inherent in many blood glucose variability measures: their insensitivity to hypoglycemia and their inherent bias toward hyperglycemic readings. This problem is due to the asymmetry of the blood glucose scale (26) and is common for SD of blood glucose, interquartile range, MAGE, and others.

To validate the ADRR, we have taken two steps. First, the ADRR was constructed using a development dataset, and all its parameters and category cutoffs were fixed. Then, the ADRR was tested in a large independent validation dataset against a comprehensive variety of standard and previously reported in the literature measures of average glycemia and blood glucose variability, including A1C, mean, SD, and CV of blood glucose, M-value, MAGE, interquartile range, and lability index. The results were consistent between the development and the validation data and showed that the properties of the new measure corresponded well to the major feature embedded in its design: equal sensitivity to future extremely low and high blood glucose values. Thus, if we accept the fact that the criterion for efficiency of a measure is its accuracy in predicting future hypoglycemia and hyperglycemia, the ADRR is superior to all (to the best of our knowledge) previously introduced variability measures. Below is a summary of the clinical advantages evident from the testing of the ADRR and of the numerical properties underlying its design:

1) Because it is based on the normalized blood glucose scale, the ADRR is similarly predictive of future hypoglycemia and hyperglycemia. Most importantly, the ADRR predicts the consequences of glycemic variability equally well in type 1 and type 2 diabetes; once an individual attains a certain risk level (ADRR category), the percentage of future normoglycemia is no longer dependent on the type of diabetes.
2) Because risk values are used instead of blood glucose values, the target blood glucose range is given less weight; thus, blood glucose variation within

Table 2—*Frequency of future hypoglycemia, blood glucose values in target range, and hyperglycemia stratified along the categories of ADRR*

BG range ADRR (mmol/l)	Hypoglycemia: BG <3.9	Target: 3.9 ≤ BG ≤ 10	Hyperglycemia: BG >10
Low risk (20% of subjects)			
ADRR <10	66 (3.8)	1,430 (83.3)	220 (12.8)
10 ≤ ADRR < 20	213 (6.8)	3,025 (63.9)	920 (29.3)
Moderate risk (52% of subjects)			
20 ≤ ADRR < 30	638 (10.2)	3,025 (48.6)	2,565 (41.2)
30 ≤ ADRR < 40	1,392 (15.8)	3,898 (44.3)	3,519 (39.9)
High risk (28% of subjects)			
40 ≤ ADRR < 50	870 (16.2)	1,909 (35.5)	2,592 (48.3)
ADRR ≥ 50	843 (22.6)	1,265 (33.9)	1,619 (43.4)

Data are *n* (%). BG, blood glucose.

target will contribute less to the ADRR than excursions outside of this range. This corresponds to the clinical understanding that fluctuations within target are generally benign.

3) More extremely low and high blood glucose values contribute progressively to increasing the ADRR, which corresponds to the clinical impression that lower hypoglycemic values or higher hyperglycemic values carry increasing risk for the patient. This particular point contrasts the risk-based ADRR to the traditional counting of hypoglycemic or hyperglycemic episodes that does not take into account the extent of these conditions.
4) The ADRR is not a relative measure (unlike SD, which is relative to the mean); thus, it can be given clearly defined cutoffs, i.e., the risk categories identified in this article.
5) The ADRR uses routine SMBG data, and its computation is no more complex than that of average daily blood glucose range or the lability index (28). Thus, the ADRR can be incorporated into spreadsheets (e.g., Excel), diabetes management software, low-power computers (e.g., pocket PCs), or directly in SMBG devices that have data processing capabilities.

In summary, as a measure of glycemic variability that could be calculated frequently and tracked over time, the ADRR has promise in facilitating the provision of clinically relevant information to patients and clinicians. Future studies will determine whether regular feedback about ADRR to patients and/or their clinicians will result in improvements in glycemic control.

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