Glucose Variability

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The proposed contribution of glucose variability to the development of the complications of diabetes beyond that of glycemic exposure is supported by reports that oxidative stress, the putative mediator of such complications, is greater for intermittent as opposed to sustained hyperglycemia. Variability of glycemia in ambulatory conditions defined as the deviation from steady state is a phenomenon of normal physiology. Comprehensive recording of glycemia is required for the generation of any measurement of glucose variability. To avoid distortion of variability to that of glycemic exposure, its calculation should be devoid of a time component. ***Diabetes*** **62:1398–1404, 2013**

The salutary effect reported in the Diabetes Control and Complications Trial (DCCT) (1) and the UK Prospective Diabetes Study (2) on the development and progression of microvascular complications of diabetes has been ascribed to reduced glycemic exposure. This interpretation has been challenged (3) as overlooking the potential for additional benefit accruing from reduced glycemic variability. Its proponents have emphasized the meager ~11% variation in retinopathy risk attributable to glycemic exposure in the DCCT (4) while minimizing the 96% treatment effect attributable to HbA_{1c} (5). The limitations inherent to retrospective analyses notwithstanding, several have reported no effect of glucose variability in the DCCT (6–8). Oxidative stress, the putative mediator of diabetes complications (9), has been reported to be greater for intermittent as opposed to sustained hyperglycemia under experimental conditions (10) with qualified confirmation in clinical studies (11,12). The potential role for glycemic variability in the genesis of diabetes complications appears, therefore, to be an open question.

Implicit in the premise that variability is the deviation from steady state is the acknowledgment that a modest degree of variation of glycemia is characteristic of normal glucose homeostasis. Although linked glucose variability must be distinguished from glycemic exposure. Glycemic variability mandates restriction to a description of glucose excursions exclusive of a time component. Glucose excursion × time = glycemic exposure. Glucose excursion/time = slope is an indicator of rate of glucose change but not its extent. Consider two identical glucose excursions differing in duration by a factor of 2: the distortion of variability varies from twofold to fourfold when time is used as a multiplier or divisor, respectively.

Differences in the unpredictability of glycemia, recognized once insulin became available in the early 1920s, found partial explanation in the characterization by Himsworth (13) in 1936 of diabetes as insulin sensitive or insulin insensitive. Variation in lability of glycemia was confirmed in subsequent studies that quantified glycemic behavior in the assessment of the effectiveness of modified insulins (14–16). In those reports and others (17) committed directly to the measurement of glycemic variability, various manipulations of intermittent blood and urine glucose determinations amounted to crude estimates of a combination of within-day (nyctohemeral) and between-day glycemic behavior. None has endured, presumably because of incomplete ascertainment of glycemia. Day-to-day glucose variability devolves primarily to a comparison of differences in mean glycemia or its surrogates and as such is phenomenologically different from nyctohemeral variability and will not be discussed here.

MEASURES OF GLUCOSE VARIABILITY

M-value. The M-value of Schlichtkrull (18,19) has proven to be a durable nyctohemeral measurement of glycemic behavior. It was the mean of the logarithmic transformation of the deviation from a reference value of six blood sugar (BS) measurements taken over a 24-h period plus an amplitude correction factor (Table 1). The latter is the difference between maximum and minimum BS values for the 24-h period divided by 20 (W/20). In the following formula, PG is plasma glucose.

$$\text{M-value} = \frac{\Sigma}{N}\left|\text{M}\frac{BS}{BS}\right| + \text{W}/20 \quad \text{where} \quad \text{M}\frac{BS}{BS} = \left|10\log\frac{PG}{120}\right|^3$$

The formula gives greater emphasis to hypoglycemia than hyperglycemia. The choice of 120 mg/dL as the reference value is somewhat puzzling since the intent of the creators of the M-value was to determine "the difference between the observed blood sugar and normal blood sugar" (18), which was 95 mg/dL in their reference group of normal patients (20). A plausible explanation is that the M-value was generated initially from data of persons with diabetes and a margin of safety was permitted. Fidelity to the original intent of the M-value warrants using a reference value consonant with basal glycemia in normal subjects, e.g., 80 for whole blood (21) and 90 for plasma measurements of glucose (22) (Table 1). When this principle is applied, comparisons among various studies can be done as long as the reference value for each study in question uses the normal basal glucose value as determined by local methodology. When 25 or more glucose values are obtained over a 24-h period, the amplitude correction factor can be eliminated (23). Unfortunately, the M-value is not an indicator solely of glucose variability but is a hybrid measure of both variability and mean glycemia.

Mean amplitude of glycemic excursions. The development of continuous in vivo blood glucose (BG) analysis in the 1960s eliminated the shortcomings of intermittent discrete BG sampling (24). Application of this methodology

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DOI: 10.2337/db12-1396

See accompanying article, p. 1405.

TABLE 1
M-value of Schlichtkrull

Glucose (mg/dL)	M $\frac{BS}{BS}$*	Glucose (mg/dL)	M $\frac{BS}{BS}$	Glucose (mg/dL)	M $\frac{BS}{BS}$
0		100	0	200	42
5		105	0	205	46
10		110	0	210	50
15		115	1	215	54
20		120	2	220	59
25	172	125	3	225	63
30	109	130	4	230	68
35	69	135	6	235	72
40	44	140	7	240	77
45	27	145	8	245	82
50	17	150	11	250	87
55	9	155	14	255	93
60	5	160	16	260	98
65	3	165	18	265	103
70	1	170	21	270	109
75	0	175	24	275	114
80	0	180	27	280	120
85	0	185	30	285	125
90	0	190	33	290	131
95	0	195	38	295	137

The M-value has been modified from the original reference value of 120 mg/dL to 90 mg/dL to reflect normal basal glycemia when glucose is measured by a specific method on plasma. When there are >25 glucose values/24 h the amplitude correction factor W/20 can be eliminated. $*M\frac{BS}{BS} = \left|10\log\frac{PG}{90}\right|^3$ $\text{M-value} = \frac{\Sigma}{N}\left|M\frac{BS}{BS}\right| + W/20$

was pursued in only a few centers worldwide and often only for descriptive purposes (25,26). In contrast, G.D. Molnar of the Mayo Clinic dedicated this tool to the furtherance of his longstanding interest in the quantification of "brittle diabetes" (17,27). Since the ultimate goal in the treatment of diabetes is the restoration of glycemia to that of persons without diabetes, the Mayo group argued that the generation of a metric of glycemic excursions should begin with an examination of the profiles of nondiabetic individuals. Furthermore, such a measure should be simple in concept and faithful to the physiological basis for the glucose swings. To do otherwise would condemn the endeavor to the fruitless task of bringing order from the chaos of the glucose profiles characteristic of type 1 diabetes and risk failure to establish biological relevance.

Because interest lay in the amplitude of glycemic swings and not in the dispersion of all the glucose data, SD was considered to be unsuitable. Because glycemic excursions in normal subjects occurred solely in response to food ingestion (Fig. 1), their recognition required a criterion exclusive to the meal-related glycemic responses. Use of an absolute value of BG such as 25 mg/dL or 50 mg/dL as a criterion for a glucose swing was abandoned because each failed to account for all of the meal-related nondiabetic glucose excursions. Upon reflection, an absolute value of BG was an ill-conceived benchmark because it failed to recognize that even among normal subjects the responses to identical food-related perturbations may result in differing glucose elevations. The criterion, which did recognize all of the meal-related glucose excursions for all of the normal subjects, was the SD of the mean BG for each 24-h period of study (288 values taken q5min from the continuous record) for each individual (Fig. 1). In contrast, 0.5 SD and 1.5 SD were less inclusive/exclusive. Although the numerical value of 1 SD will perforce differ in absolute value from person to person, it nevertheless acts as an individualized standard. By convention, a glycemic excursion (both trough-to-peak and peak-to-trough) must exceed 1 SD of the respective 24-h BG profile. For continuous recordings exceeding 24 h, the use of 1 SD calculated for the whole period of study may result in the inclusion of the same excursions as use of the separate 24-h SDs, since SDs from successive days do not differ by

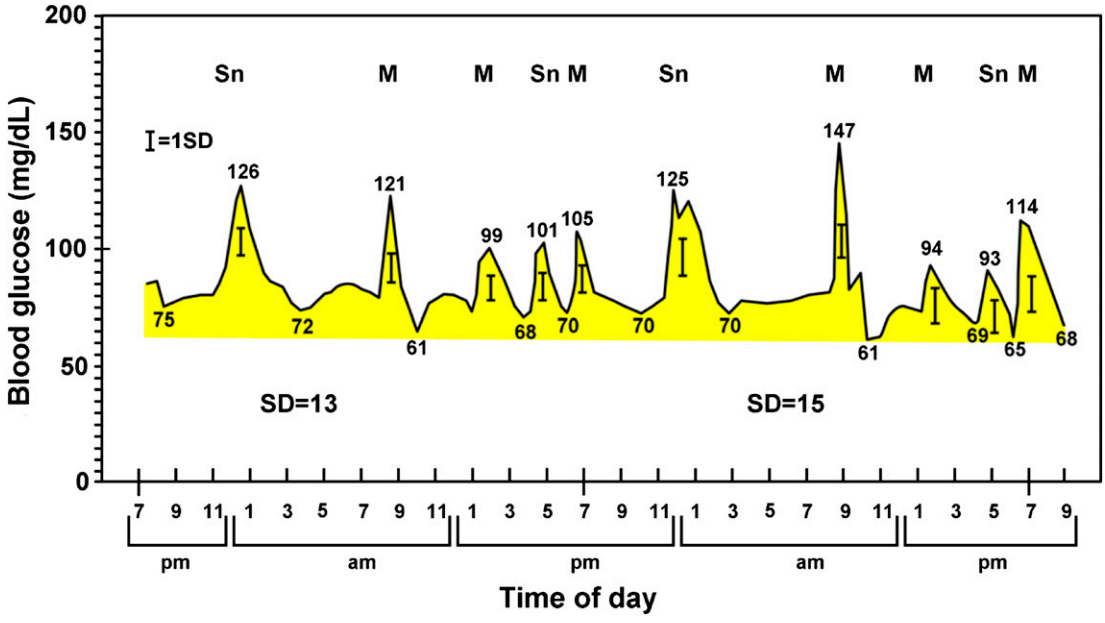

FIG. 1. Continuous BG analysis for 48 h in an ambulatory fed normal subject. The timing and frequency of food ingestion matches that of the type 1 diabetic patient in Fig. 2. Note that each glucose excursion occurs in response to food ingestion and that each limb, ascending and descending, exceeds 1 SD of the 288 data points/24 h taken every 5 min from the 48-h tracing. Note the small difference in SD between days 1 and 2. Mean BG was 84 and 82 mg/dL and MAGE 41 and 48 for days 1 and 2, respectively. M, meal; Sn, snack.

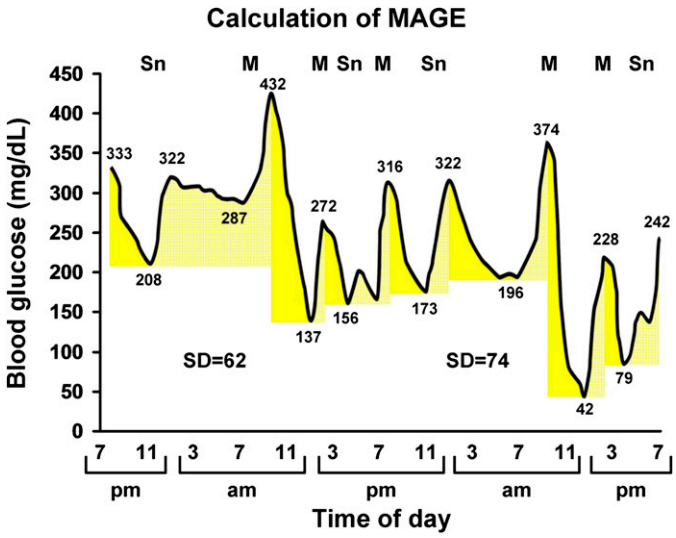

FIG. 2. Continuous BG analysis for 48 h in a patient with type 1 diabetes. The qualifying excursions are shown as pairs of solid and stippled yellow beginning with the leftmost deflection, 333 to 208 mg/dL. The inflection component of that excursion is 208 to 432 mg/dL, which incorporates an intermediary excursion. The latter fails to qualify as an excursion on its own because one limb (322 to 287 mg/dL) fails to exceed 1 SD for that 24-h period. Note the small difference in SD from day 1 to day 2. Whether MAGE is calculated from the descending (184 mg/dL) or ascending (171 mg/dL) limbs, the values are similar. M, meal; Sn, snack.

much (even in type 1 diabetic patients as long as therapy has not changed during the period of monitoring) (Fig. 2). Only one limb of the excursion, ascending or descending, determined by the initial excursion (which is not always an inflection especially in type 1 diabetic patients) is used for calculation of subsequent excursions.

Glycemic excursions of the same magnitude may qualify for one subject but not for another should the SD of the latter be larger than that of the former. The excluded excursion is not lost, however, but is incorporated into a larger one of which it is a part. Whether this is problematic is unknown. Should the subsumed excursion be of a magnitude observed for normal subjects its exclusion may be inconsequential relevant to the risk for the development of microvascular complications of diabetes. The arithmetic mean of the glycemic excursions for the period of study (24 h, 48 h, or longer) is the value of mean amplitude of glycemic excursions (MAGE) (21).

An automated algorithm has been created for the calculation of MAGE (28). Although created for determination from continuous BG analysis, MAGE has been applied to intermittent (7- and 22-point sampling/24 h) measurements (6,29) as well as continuous interstitial glucose monitoring (30).

SD. SD is a commonly reported expression of glucose variability. Its ease of calculation and possible concern that its absence would impugn authors' commitment to a comprehensive assessment of variability drives its inclusion in virtually all articles on this topic. SD is not a fallback measure by any means; it does have vigorous support (31). Unfortunately its utility is hampered by the lack of Gaussianness of glucose profile data (Fig. 3) and the potential for widely different glycemic curves having the identical numerical value of SD (32).

J-index. The J-index perpetuates the inclusion of SD into the measurement of glycemic variability. Originally derived from intermittent BG determinations, it has been adapted to continuous monitoring data. Its proponent recommends it as a measure of both the mean level and variability of glycemia (33). This parameter has not been widely used. In the following formula, MBG is mean BG.

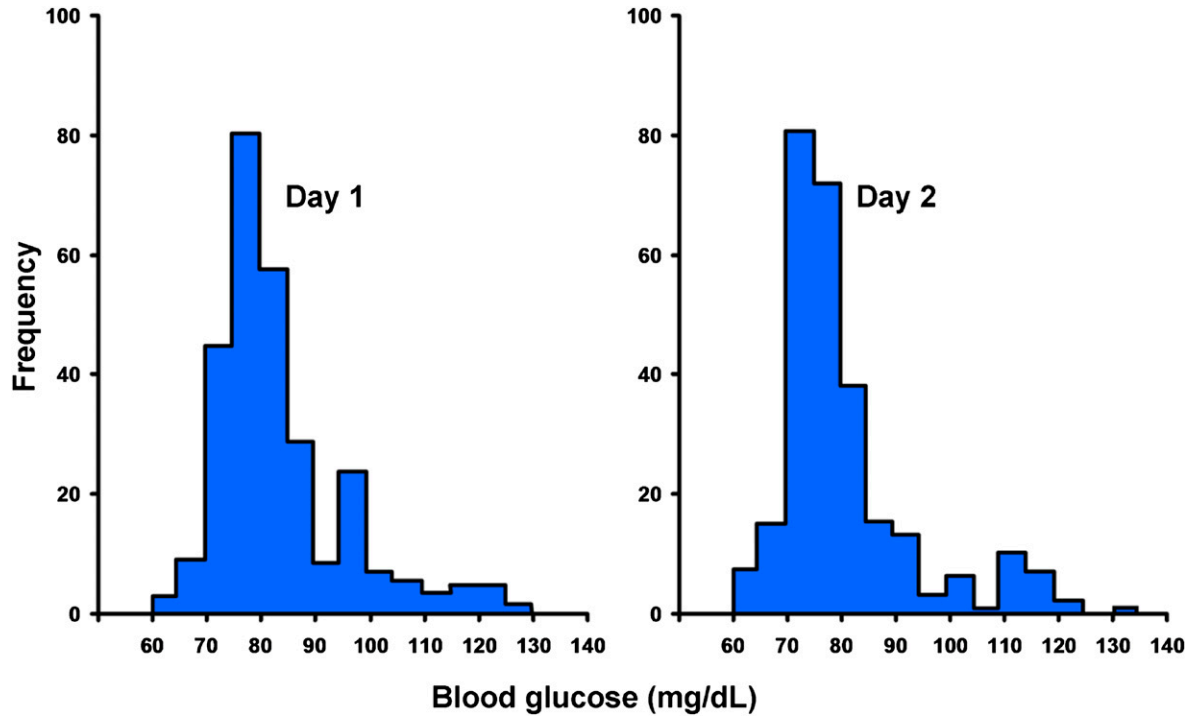

FIG. 3. Frequency distribution of the 576 glucose values/48 h from Fig. 1 plotted per 24-h period showing a lack of normal distribution.

$J = 0.001(MBG + SD)^2$ for glucose measured in mg/dL
$J = 0.324(MBG + SD)^2$ for glucose measured in mmol/L

Mean absolute difference, mean absolute glucose, and continuous overall net glycemic action *n*. Three parameters based on the analyses of sequential BG values have been proposed as measures of glycemic variability. The mean absolute difference (MAD) of consecutive BG values was derived from self-monitored BG data performed five times per 24 h (34). The authors have acknowledged that MAD has no advantage over SD as an estimate of glycemic variability.

Mean absolute glucose (MAG) is the summed differences between sequential 7-point self-measured BG profiles per 24 h divided by the time in hours between the first and last BG measurement (35). A limitation to MAG is that two excursions of identical extent but of different duration have different values.

Continuous overall net glycemic action (CONGA) n, was conceived for continuous interstitial glucose monitoring. Analysis requires a complete tracing, i.e., 288 values per 24 h. For each glucose datum after the first n hours of observations, the difference between the current glucose and the glucose n hours previous is determined. n can vary from 1 to 8 h. For instance, for $n = 1$ and 24-h period of monitoring beginning at 0800, the calculations would begin as follows: BG at 0900 minus BG at 0800; BG at 0905 minus BG at 00805; BG at 0910 minus BG at 0810 and so on until BG 0800 (the next day) minus BG at 0700 (Fig. 4). The period of analysis is 24 h minus n. CONGA is expressed as the SD of the differences despite their lack of normal distribution (Fig. 4) (36).

For none of these parameters—MAD, MAG and CONGA n—has a rationale been promulgated to support its use. Since each was based on examinations of tracings from patients with diabetes rather than normal subjects, it is difficult to assign any biological relevance to them. Reliance solely on mathematical manipulations to the exclusion of relevance is analogous to the feckless statistician who drowned wading across a river whose average depth he calculated to be 4 feet: failure to appreciate the relevance of the variation in water depth from shore to shore was his undoing.

Inclusion of all data points fails to discriminate glycemia directly related to excursions from that which might be considered as noise. Furthermore, it is difficult to identify a biorhythm with periodicities of 1, 2, 3, or more hours implicit in the generation of CONGA n.

Postprandial glycemia. For postprandial hyperglycemia to play a role in the development of diabetes complications, its influence must exceed its contribution to mean glycemia. Otherwise the effect of improved mean glycemia is amenable to study with techniques less arduous than the task of controlling postprandial hyperglycemia (37). Implicit in the putative special role for postprandial glucose is the assumption of unique properties associated with the meal-related glucose excursion not attendant upon hyperglycemia of a similar degree in the interprandial state (10,11). A clinical trial designed to assess the effect of postprandial glucose on the development of diabetes complications must ensure no difference in HbA_{1c} or mean glycemia while generating a difference in postprandial glycemia. To achieve these goals, the interprandial glucose would of necessity have to increase, thereby resulting in reduced glucose excursions (38). When measured in this context postprandial glucose therefore takes on the mantle of a surrogate for glycemic variability.

Assessment of postprandial glycemia poses not just a difficult but a virtually impossible task when limited to one after-meal determination: a static measurement in

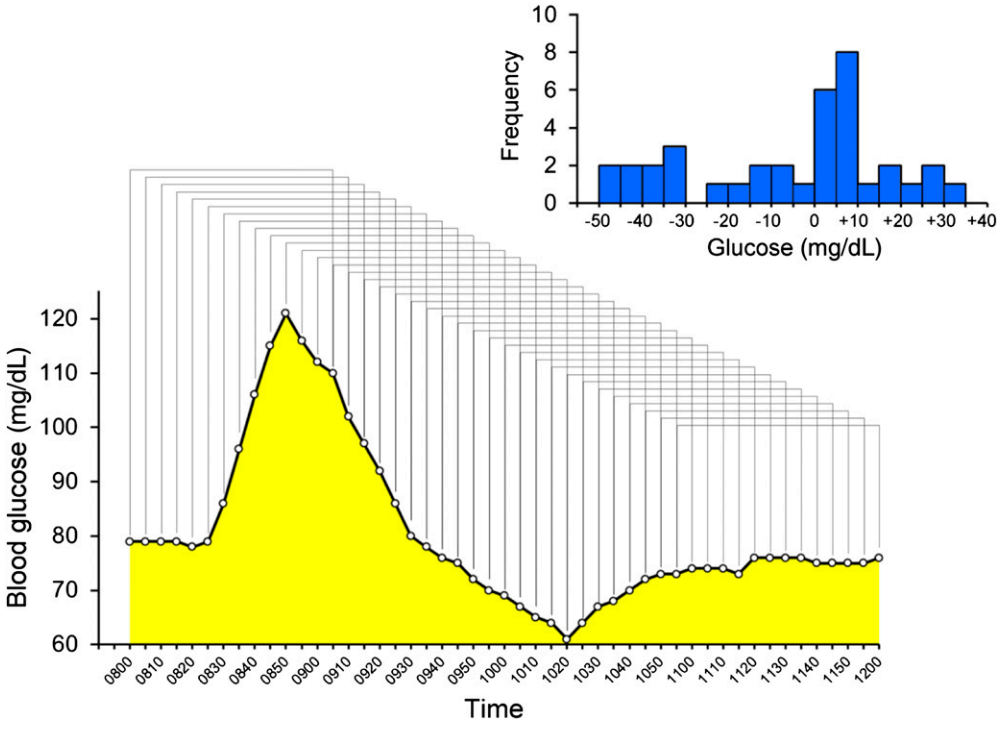

FIG. 4. CONGA *1* analysis for the breakfast meal day 1 from Fig. 1. For illustration purposes only 4 h are shown. For this period, the mean of hourly differences determined at 5-min intervals is −5.5 mg/dL with an SD of 22.2, which is the actual CONGA value. The insert shows the frequency distribution of the sequential glucose differences, which clearly does not have a normal distribution.

a dynamic situation. In persons without diabetes, glucose responses to food ingestion are influenced by the size, composition, and time of day of the meal (39,40). The responses in patients with diabetes are more variable (41). Even in the situation of complete ascertainment from continuous glucose monitoring, reliance on peak postprandial glucose as a measure of variability is fraught with potential error because it represents only the north end of the meal-related excursion; without the south end there is no actual excursion. Without documentation of the starting point of an excursion its size cannot be known.

Low BG index, high BG index, and glycemic risk assessment diabetes equation. Two quantifications of risk for hypoglycemia and hyperglycemia have been reported under the rubric of glucose variability (42,43). High BG index (HBGI) and low BG index (LBGI) are generated from a correction of the skewness of glycemia (narrow hypoglycemic vs. broad hyperglycemic range) through a symmetrization process around zero (equivalent to glucose 112.5 mg/dL) by expanding the hypoglycemic range and reducing the hyperglycemic range (42).

$$LBGI = \frac{1}{n}\sum_{i=1}^{n} rl(\chi_i)$$

$$HGBI = \frac{1}{n}\sum_{i=1}^{n} rh(\chi_i)$$

$$f(\mathrm{BG}) = 1.509 \times \left[(\ln(\mathrm{BG}))^{1.084} - 5.381\right] \quad \text{for BG in mg/dL}$$

$$f(\mathrm{BG}) = 1.509 \times \left[(\ln(18 \times \mathrm{BG}))^{1.084} - 5.381\right] \quad \text{for BG in mmol/L}$$

$$r(\mathrm{BG}) = 10 \times f(\mathrm{BG})^2$$

$$rl(\mathrm{BG}) = \mathrm{r(BG)} \quad \text{if } f(\mathrm{BG}) < 0 \textit{ and } 0 \text{ otherwise}$$

$$rh(\mathrm{BG}) = \mathrm{r(BG)} \quad \text{if } f(\mathrm{BG}) > 0 \textit{ and } 0 \text{ otherwise}$$

The rationale for this maneuver is not stated nor is it readily inferred since risks associated with hypoglycemia are different from those associated with hyperglycemia in type, timing, and predictability, and they have no interaction. Larger values of LBGI and HBGI indicate higher risk for hypoglycemia and hyperglycemia, respectively. Although originally developed from self-monitored BG data, these parameters have been adapted to continuous interstitial glucose monitoring (44). Correlations between LBGI and subsequent hypoglycemia and between HBGI and HbA_{1c} have been reported.

The glycemic risk assessment diabetes equation (GRADE) score was created to summarize the degree of risk associated with a glucose profile (43). Qualitative risk scoring for a wide range of glucose levels inclusive of marked hypoglycemia and hyperglycemia was generated by a committee of diabetes practitioners. The nature of the risk was not specified. In the determination of GRADE, glucose values are transformed to yield a continuous curvilinear response with a nadir of 90 mg/dL and high adverse weighting to hyperglycemia and hypoglycemia.

$$\text{mmol/L GRADE value} = 425x\,[\log[\log(X)] + 0.16]^2$$

$$\text{mg/dL GRADE value} = 425x\,[\log[\log(X \times 18)] + 0.16]^2$$

$$\text{where } X = \text{blood glucose}$$

Since a high GRADE score may be generated from either hyperglycemia or hypoglycemia, the range of glucose contributing to the score is reported as percentages: <70 mg/dL (hypoglycemia), 70–140 mg/dL (euglycemia), and >140 mg/dL (hyperglycemia).

Neither LBGI/HBGI nor GRADE measures glucose fluctuations directly. Since both manipulations use all of the available glucose data, the highly derivatized results appear to be an expression of quasi mean glycemia (LBGI/HBGI) or a frequency distribution (GRADE). Unfortunately, the term "risk" may not serve these parameters well, especially in the context of predicting future events. An undesirable value of LBGI, HBGI, or GRADE should lead to an immediate change in therapy for the purpose of mitigating future adverse events rather than act as predictors in the face of persistent flawed treatment.

1,5-anhydroglucitol. This substance has been proposed as a surrogate marker for glycemic excursions (45). Once circulating glucose levels exceed the renal threshold for glucosuria plasma, levels of 1,5-anhydroglucitol (all because its renal reabsorption is competitively inhibited by glucose. Distinction between chronic and intermittent hyperglycemia, both of which are characterized by low concentrations of 1,5-anhydroglucitol, is governed by the HbA_{1c} level, which when normal or near-so suggests intermittent forays of glycemia into the hyperglycemic range, i.e., large glycemic excursions. There are several limitations of 1,5-anhydroglucitol as a measure of glycemic variability. It does not measure glucose fluctuations directly and therefore cannot determine their size and frequency or those occurring below a BG ~180 mg/dL and is not useful when the HbA_{1c} level is elevated.

GLUCOSE VARIABILITY AND THE COMPLICATIONS OF DIABETES

There have been no randomized clinical trials directed at this question despite inferences from secondary analyses (6–8). Although the Hyperglycemia and Its Effect After Acute Myocardial Infarction on Cardiovascular Outcomes in Patients With Type 2 Diabetes Mellitus (HEART2D) trial, which compared prandial to basal glucose control, was (38) not specifically designed to evaluate glycemic variability, inferences can be drawn from the narrower range of glucose values in the prandial wing. A retrospective analysis concluded that improved glycemic variability (lower MAG with no differences in SD or MAGE) in the prandial versus basal treatment groups had no effect on cardiovascular outcomes (46). This interpretation has been disputed partly on the basis of the exclusive reliance on MAG, an alleged unvalidated measure of variability to the exclusion of other established metrics (47). In a cross-sectional study of type 1 and type 2 diabetic patients an association was found between cardiovascular risk factors and measures of average glycemia (mean BG and HbA_{1c}) but not with measures of glycemic variability (MAGE, CONGA *4*, and postprandial glucose increment) (48). In a randomized trial in type 2 diabetes not specifically designed to address the effect of glycemic variability, lower postprandial and higher fasting glycemia led to a regression in carotid intima thickness despite no change in HbA_{1c} (49).

FUTURE

There should be no doubt that pharmacological advances directed to the ultimate goal of physiological insulin replacement will continue with the eventual development of faster-acting/shorter-duration insulins to the point where

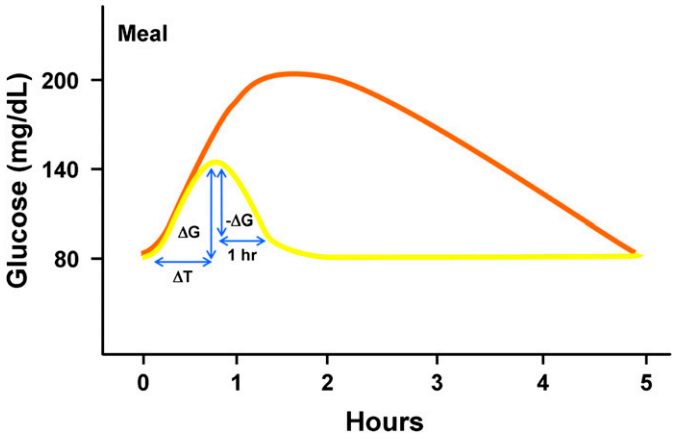

FIG. 5. The orange line is a stylized representation of the best that can be achieved currently for meal-related glucose control in diabetes. Once therapies become available to bend the postprandial curve to match that of nondiabetic subjects (yellow line), new metrics will be needed. Glucose rise to peak (ΔG), time to peak (ΔT), and % baseline recovery 1 h after peak (−ΔG/ΔG) have been used for this purpose (50). Average values for these metrics in normal subjects are ΔG = 40 mg/dL, ΔT = 45 min, and baseline recovery 1 h after peak = 90%.

the postprandial glycemic curve will be bent to conform to that of nondiabetic subjects. In that utopian situation, the currently available measures of glycemic variability can be retired. In their place, specific metrics that characterize the primary features of the meal-related excursion such as glucose rise to peak, time to peak, and timeliness of recovery to baseline glycemia would be appropriate (Fig. 5) (50).

CONCLUSIONS

Analogous to the vital role played by HbA_{1c} in testing the "glucose hypothesis" is the need to establish an accurate and biologically relevant modality to test the "glycemic variability hypothesis." Each of the published quantifications of glucose variability has its limitations, some so significant to vitiate utility. Unlike the integrated measure of long-term glucose control provided by a single quarterly determination of HbA1c glycemic variability by nature requires comprehensive assessment of glycemia. Whereas continuous BG analysis provides an accurate recording of glycemia during ambulatory fed conditions it has not been adapted to the free-living state. Although not constrained by that limitation, continuous interstitial glucose monitoring is hampered by variable and unpredictable inaccuracies (51). The task therefore, of assessing a role for glycemic variability in the development of diabetes complications is fraught with difficulty. The question may ultimately prove to be moot should elimination of the complications of diabetes ensue from the bending of the prandial glycemic curve to that of nondiabetic subjects.

ACKNOWLEDGMENTS

No potential conflicts of interest relevant to this article were reported.

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