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Editorial

Glycemic Variability: Measurement and Utility in Clinical Medicine and Research—One Viewpoint

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One cannot control average glucose levels unless one first reduces glycemic variability! This sounds intuitively obvious[1,2] and can also be demonstrated rigorously, mathematically.[3] If the mean glucose level were 100 mg/dL but the SD were 40 mg/dL, one could predict that there would be an unacceptable incidence of severe hypoglycemia even though the mean glucose is in the euglycemic range. Clinicians must understand glycemic variability both qualitatively and quantitatively and endeavor to reduce that variability before trying to reduce the mean level of blood glucose. This applies to blood glucose as measured by self-monitoring of blood glucose (SMBG), laboratory measurements of venous samples or arterial blood, and interstitial glucose as measured by continuous glucose monitoring (CGM). When titrating a medication such as basal insulin, it is essential to know the between-day (*within-subject*) variability in fasting plasma glucose to be able to set the target glucose level appropriately so that risk of hypoglycemia is at an acceptable level. Unfortunately, these estimates of glycemic variability are rarely obtained. Glycemic variability also serves as one facet of the *quality of glycemic control*—another reason to quantify glycemic variability.

Theoretical and preclinical studies suggest the possibility that glycemic variability might contribute to the risk of complications in diabetes.[1,4–10] This hypothesis remains controversial and will remain an active area of research.[11–20]

The above three considerations—the requirement to achieve good control, the desire to assess quality of glycemic control, and the plausible link to complications[1,4–20]—provide a major impetus for development, testing, and application of methods to quantify glycemic variability.

If the distribution of blood glucose were Gaussian or "normal"—a symmetrical bell-shaped curve with completely defined mathematical properties—then characterization of variability would be simple: we could just use the SD. However, glucose distributions come in a wide variety of shapes, usually "skewed to the right." Several authors[2,21–26] have proposed use of methods that are not dependent on the assumption of normality (e.g., use of the maximum, minimum, 75^{th} and 25^{th} percentiles, and the interquartile range [IQR], where IQR is the difference between the 75^{th} and 25^{th} percentiles). However, *if* the distribution were Gaussian, then there would be a simple relationship between the IQR and SD: $IQR = 1.35 \times SD$.[2] Because of the consistent shape of the glucose distribution in many circumstances, it is often possible to transform the glucose scale so that it becomes nearly symmetrical and nearly Gaussian.[2] Kovatchev et al.[21] used a transformation designed to impart symmetry to the glucose distribution, and this in turn provides the foundation for the Low Blood Glucose Index (LBGI) and the High Blood Glucose Index (HBGI), which were later combined into the Average Daily Risk Range (ADRR) and the Blood Glucose Risk Index (BGRI).[21,24,25] Rodbard[26–28] sought to find a simpler mathematical expression. Use of log(Glucose + constant), where the constant might be a small value such as 15 mg/dL, or $(\text{Glucose} + \text{constant})^{(1/n)}$ [e.g., use of the fourth root of (Glucose + constant)] dramatically reduces the asymmetry of the glucose distribution. (Asymmetry is quantified by skewness, or skew, readily calculated in spreadsheets and statistics packages.) He also attempted to find a simpler mathematical expression to express the risk of hypoglycemia and hyperglycemia than the LBGI and HBGI, leading to development of the Hypoglycemic Index and Hyperglycemic Index.[26–28] Using a related approach, Hill et al.[29] obtained the input from a wide range of clinicians regarding their subjective numerical estimates of the deleterious effects or hazards of hypo- and hyperglycemia and then created a mathematical expression (again, closely related to a log scale) to describe that relationship. They used that scale to derive a score to assess the quality of glycemic control for SMBG data, and this has subsequently been applied to CGM data.[30,31] The methods of Kovatchev et al.,[21,24] Clarke and Kovatchev,[25] Rodbard,[26–28] and Hill et al.[29] result in a similar transformations of the glucose scale, to the extent that it is likely to be extremely difficult to differentiate among these three alternatives.[32] (Rodbard[26,27] provides a series of methods because he allows the users to change parameters that control the relative weights given to hypo- and hyperglycemia. Kovatchev has also modified his original method to attempt to make it more appropriate to assess diabetes during pregnancy [see Zisser et al.[33]].)

Theoretically, these three approaches—{HBGI, LBGI, ADRR, BGRI}, {Hypoglycemia Index, Hypoglycemia Index, Index of Glycemic Control}, and {Glycemic Risk Assessment Diabetes Equation (GRADE), $GRADE_{HYPOGLYCEMIA}$, $GRADE_{HYPERGLYCEMIA}$}—should be superior to simple use of the percentages of glucose values within specified ranges (e.g., <70, 70–180, and >180 mg/dL). The indices retain the use of a

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continuous scale for glucose so that glucose values of 69 and 71 mg/dL are regarded as nearly equivalent rather than in separate qualitative categories. These indices also deal appropriately with the fact that values of 40 and 69 mg/dL should be given very different scores and not be labeled simply as "hypoglycemia" or " <70 mg/dL."

To assist the clinician with the interpretation of measures of glycemic variability, we need to have "normative" or "reference" data. Data on normal individuals, as reported by Mazze et al.[23] and Zhou et al.,[34] are helpful in setting a baseline. However, these values are so far removed from what is observed in patients with diabetes that they have only minimal relevance. (One can use these values to evaluate changes in patients with diabetes, for example, addressing the question: "What percentage of the difference between his or her initial value and the center of the range for normal subjects [without diabetes] has a patient achieved in response to therapy?") We need to be able to assess the observed variability in a large population (or populations) of people with diabetes. Even a reference sample based on 50–100 subjects can be helpful. The physician can then compare any given patient with other patients with the same type of diabetes being treated in the same office, clinic, or institution and determine whether the patient is doing better or less well than average. With a larger data set, one can divide the population into four or five groups—quartiles or quintiles.[28] When using quartiles, we might designate the four categories as "much better than average" (Excellent), "better than average" (Good), "somewhat less well than average" (Fair), and "much less well than the average" (Poor). Criteria for such ratings can be developed for different subsets of patients. Because most measures of glycemic variability change systematically with mean glucose level and glycosylated hemoglobin (A1C) level, criteria can be developed for multiple ranges for mean glucose or A1C levels. When we apply this type of analysis to a group of patients with diabetes, we obtain an empirical basis for interpretation of measures of glycemic variability.[28] This analysis needs to be repeated for multiple subsets of patients, preferably using larger and more comprehensive patient samples from a defined population (e.g., all patients with type 2 diabetes being treated within a specified healthcare system, clinic, or academic setting). Small clinical organizations can also collect and analyze these kinds of data by adopting the same kinds of approaches as used by clinical chemistry laboratories to establish reference ranges. We can convert all of the different types of measurements of glycemic variability into *percentiles relative to a defined patient population*, expressing them on a simple consistent numerical scale from 0 to 100%. (This is similar to "marking on the curve" for test results in academic settings.) We can then calculate averages of any selected set of parameters.

An "Index of Glycemic Variability"

We seek to be able to combine information from several measures of glycemic variability, specifically, (1) the overall or *total* SD of glucose, SD_T, (2) the SD of glucose *within days*, SD_w, (3) the SD of *daily means*, SD_{dm}, (4) the SD *between days* (for glucose at a specified time of day) after correction for the variation in the daily mean glucose, $SD_{b\ //\ dm}$, and (5) a measure of the stability of the glucose pattern by time of day over the course of a week. (For example, one can use the following index of stability of the glucose pattern: the SD of [Observed glucose at any given time of day for each of the days in the series]/[Predicted glucose at the corresponding time of day, based on the average glucose at that time of day, for all of the days in the series].) Each of these five measures can be expressed as a *percentile score relative to a defined patient sample*.[28] One can then calculate the average of the percentile scores for each of these five criteria to obtain an overall score. This score provides an overall "Index of Glycemic Variability," an IGV. Other combinations of indices could potentially be used. The SD of the five percentile scores provides a measure of the concordance of the individual components of this index.

Researchers using CGM have been trying to obtain the "best" overall index of glycemic variability for some time. We would all like to have one such measure rather than the several just mentioned or more than 20 others that have been described (e.g., continuous overall net glycemic action [$CONGA_n$], mean of daily differences [MODD], mean amplitude of glucose excursions [MAGE], mean absolute glucose change [MAG]) and still others that can be readily imagined (e.g., various measures of postprandial excursions). It remains to be seen just how much weight should be given to each of these parameters. Until we have much more extensive data, the methods to combine information from the various indices or parameters will remain arbitrary. There is no one *unique* answer. Nevertheless, based on clinical research studies, we may be able to identify systems for weighting of the criteria so as to generate the best predictors for specified clinical events or complications, for example, macrosomia in offspring of mothers with diabetes, "oxidative stress," and macrovascular or microvascular complications.

There is usually a very strong correlation of the magnitude of glycemic variability, irrespective of how it was measured, with the mean glucose value and with A1C. This makes it difficult to distinguish between the biological effects of mean glucose and the biological effects of glycemic variability. When looking for such effects, we must use a multivariate or multiple regression model,[13] for example,

$$\text{Biological effect or pathophysiological effect} = a + b\ (\text{mean glucose}) + c\ (\text{glycemic variability})$$

Several groups have developed computer programs and spreadsheets to calculate glycemic variability. These include methods for calculation of MAGE,[35,36] software called a "GlyCulator,"[37] and spreadsheets to calculate various types of SDs,[30,31] among others. It is hoped that this should lead to some degree of standardization and reduce the risk of errors in the computations. Furthermore, it should facilitate examination of the relationships among these parameters, several of which are highly correlated and redundant.[26,27,30,31,35] For example, there is a very high degree of correlation of both MAGE and MODD with the SD.[19,26,27,30,31,35] If that is indeed the case, then one could potentially simply use the SD and values derived from it such as the percentage coefficient of variance or the J index[38] rather than going to the trouble of making additional calculations such as the MAGE or MODD. However, the various parameters can behave differently under some conditions.[17] Only some parameters changed significantly when a CGM device was changed from masked to unmasked mode,[30,31] only some parameters appeared to be correlated with coronary artery calcification in a preliminary study of patients with type 1

diabetes,[16] and only one parameter was reported to be a correlate of cardiovascular death.[17] It remains to be seen which will prove to be most informative.

Research into the methods for measurements of glycemic variability is still in its infancy. However, considerable progress has been made. There are a plethora of measures of glycemic variability, and the number continues to grow.[1,4–9,39–43] We need to examine the interrelationships of these variables to identify the ones that provide the most useful information. We need to make these parameters more clinically useful, by providing reference ranges for defined types of patients (defined by type of diabetes, type of therapy, degree of glycemic control by the "gold standard" A1C).[28] Data reduction needs to be fully automated, whether the glucose data are generated from SMBG, CGM, or hospital-based systems. Computer outputs need to be standardized, and percentile scores must be provided for each parameter and for selected combinations or averages of parameters, and compared with appropriate reference populations. For care of patients, each patient can serve as his or her own control, and one can examine longitudinal changes in terms of the whole gamut of parameters: A1C, fasting plasma glucose, postprandial glucose, and measures of glycemic variability such as postprandial excursions, SD_T, coefficient of variation (%CV), SD_w, SD_b, SD_{dm}, $SD_{hh:mm}$, SD_{ws1}, MAGE, $MODD_1$, $CONGA_n$, MAG, and finally IGV.

It would be helpful if manufacturers of glucose meters and sensors would generate these parameters in their routine data processing software so that clinicians and researchers alike will become more familiar with them and be able to learn from experience which parameters are most helpful and informative when following an individual patient. It is hoped that these additional analyses would be presented in a standardized format in terms of terminology, symbols, sequence, color coding, and layout of tables and graphs, so that physicians and other caregivers will not be faced with a confusing variety of outputs and a resulting information overload. Administrators could potentially use these parameters to assess the performance of physicians and of the quality of care for their patient populations. The data can be valuable in the context of the design, performance, and analysis of clinical research studies.

Note Added in Proof

Several relevant studies have appeared subsequent to submittal of this article. Monnier et al.[39] and Qu et al.[40] have demonstrated empirically that several measures of glycemic variability are correlated with the risk of hypoglycemia, as expected theoretically.[3] Dalfrà et al.[41] reported relationships between macrosomia in offspring of diabetic mothers and various measures of glycemic variability. Hill et al.[42] report values for GRADE and several other measures of variability in nondiabetic subjects (cf. also 23,34,28). Marling et al.[43] describe two new methods to characterize glycemic variability, one of which appears to be essentially interchangeable with the 'mean absolute glucose (MAG) change' when observations are equally spaced (cf. 17).

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