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Interpretation of Continuous Glucose Monitoring Data: Glycemic Variability and Quality of Glycemic Control

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Abstract

There are a large number of measures of glycemic variability, including standard deviation (SD), percentage coefficient of variation (%CV), interquartile range (IQR), mean amplitude of glucose excursion (MAGE), mean of daily differences (MODD), and continuous overlapping net glycemic action over an *n*-hour period ($CONGA_n$). These are all highly correlated with the overall or "total" SD, SD_T. SD_T is composed of several components corresponding to within-day variability, between-day variability (between daily means and between days—within specified time points), and the interaction of these sources of variability. We identify several subtypes of SD; each is highly correlated with SD_T. Variability may also depend on time of day. Numerous measures of quality of glycemic control have been proposed, including a weighted average of glucose values (M_R) (e.g., M_{100} is M at 100 mg/dL), a measure of quality of glycemic control based on mean and SD (**J**), the Glycemic Risk Assessment Diabetes Equation (GRADE), the Index of Glycemic Control (IGC), the High Blood Glucose Index (HBGI), the Low Blood Glucose Index (LBGI), the Average Daily Risk Range (ADRR), and percentage of glucose values within specified ranges. These methods usually but not always give consistent results: they can differ widely in terms of their ability to detect responses to therapeutic interventions. Based on review of the advantages and limitations of these measures and on extensive experience in the application of these methods, we outline a systematic approach to the interpretation of continuous glucose monitoring data for use by clinical researchers and clinicians to evaluate the quality of glycemic control, glucose variability including within- and between-day variability, the day-to-day stability of glycemic patterns, and changes in response to therapy.

Introduction

Continuous glucose monitoring (CGM) generates so much data so rapidly that it can create "data overload" and overwhelm a busy clinician. There is a need for a systematic approach to review and interpret these data. In view of the evidence that glycemic variability may be related to the pathogenesis of complications in diabetes[1–3] and in view of the need to reduce glycemic variability in order to achieve desired levels of control,[4] it is important to have simple, clinically meaningful estimates of glycemic variability. Numerous indices of the quality of glycemic control and glycemic variability have been proposed previously.[5–29] There has been no consensus as to which of these is best or how these should be used in routine clinical practice. In the present report, we review several of the available indices of glycemic variability and quality of glycemic control and propose several new methods. We outline a systematic approach that can be used in clinical research and clinical practice.

Methods

We conducted a literature review[5–17,19–29] and assessed the advantages, limitations, and interrelationships among available methods for evaluating quality of glycemic control and assessing glycemic variability. We have tested these methods extensively using both real and synthetic data and developed a series of new and modified methods to evaluate several aspects of glycemic variability, quality of glycemic control, and stability of patterns from day to day.

Results

Measures of glycemic variability

Table 1 lists several measures that have been used to characterize glucose variability. These can be viewed as belonging to four groups or families of methods: (1) methods based on standard deviations (SDs) and related methods (percentage coefficient of variation [%CV], interquartile range

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[IQR])[4–7,18]; (2) methods to detect excursions (e.g., postprandial excursions), e.g., the mean amplitude of glucose excursion (MAGE)[10–12]; (3) methods based on day-to-day variability, e.g., the mean of daily differences (MODD)[11,12]; and (4) methods based on variability during relatively short segments of the glucose time series (e.g., continuous overlapping net glycemic action [CONGA], e.g., CONGA over a 4-h period [$CONGA_4$]).[15–18]

Interrelationships among measures of glycemic variability

The measures obtained using methods within each family are very highly correlated. For example, there is a direct linear relationship (a direct proportionality) of MAGE, $CONGA_1$, $CONGA_{1–24}$, and the SD for a large series of CGM data. ($CONGA_{1–24}$ as introduced by and defined by Kuenen et al.[16] and Nathan et al.[17] is the average of $CONGA_n$ for all integer values of n from 1 to 24.)

Figure 1 shows our re-analysis of data from a large multicenter international study to compare A1c with mean glucose levels,[16,17] involving 500 patients, each studied using CGM for 12 days. In view of this high degree of correlation, each of these measures is conveying essentially the same information. We have confirmed this finding using a large independent study[20] involving 85 patients with type 1 or type 2 diabetes, in excellent, good, or poor control, utilizing multiple daily injections or continuous subcutaneous insulin infusion, studied for three 1-week periods with the DexCom (San Diego, CA) SEVEN™ CGM sensor.[18,30] There was a high correlation of MAGE, MODD, and $CONGA_1$ with SD_T ($r = +0.90, +0.81$, and $+0.71$, respectively).

Multiple subtypes of SDs

We have applied the principles underlying analysis of variance and "components of variance" analysis, to show that there are several "subtypes" of SD (Table 2). Further details of the method of calculation for each of these subtypes of SD are described elsewhere.[18,30]

SD_T represents the total variability in the entire data set. If we display the data with time of day running vertically, and sequential days running horizontally, then we can calculate SDs in either the vertical or horizontal directions:

- The "vertical" SDs include the SD within each day; the average of the SDs within each day (SD_w); the SD between time points ($SD_{hh:mm}$), which is calculated for the mean glucose for any specified time of day; and the SD "within series" ($SD_{ws\ h}$) for time segments of any number of hours (h) (e.g., $h = 1, 2, \ldots, 24$). $SD_{ws\ h}$ may vary by time of day.
- The "horizontal" SDs represent variability between days. The simplest of these is the variability between daily means (SD_{dm}); we calculate the mean of all values for each day and then compute the SD of those daily means. A second approach is to calculate the SD between days but within each specified point (or narrow window) in time (e.g., 12:05:00 a.m. to 12:09:59 a.m.). We then average those SDs for all times of day, resulting in the $SD_{b\ hh:mm}$, a measure of the variability between days. Part of this overall change between days may be due to the fact that the average value for that day changed from

Table 1. Previously Proposed Measures of Glycemic Variability

	Reference
Standard deviation (SD)	4–7
Percentage coefficient of variation (%CV)	4–7
Glucose distribution	4–9
Histogram for all data or selected subsets of data	
% of values below, within, or above a specified target range	
Maximum, minimum, percentiles: 10^{th}, 25^{th}, 50^{th}, 75^{th}, 90^{th}	
Range = maximum − minimum	
Interquartile range (IQR) (75^{th}–25^{th} percentile)	
Mean amplitude of glycemic excursion (MAGE)	10–12
Mean of daily differences (MODD)	11, 12
Lability index (HYPO Index)	13, 14
$CONGA_n$	15
$CONGA_{1–24}$	16, 17

$CONGA_n$ is the SD of the difference between values obtained exactly n hours apart. $CONGA_{1–24}$ as introduced by and defined by Kuenen et al.[16] and Nathan et al.[17] is the average of $CONGA_n$ for all integer values of n from 1 to 24.

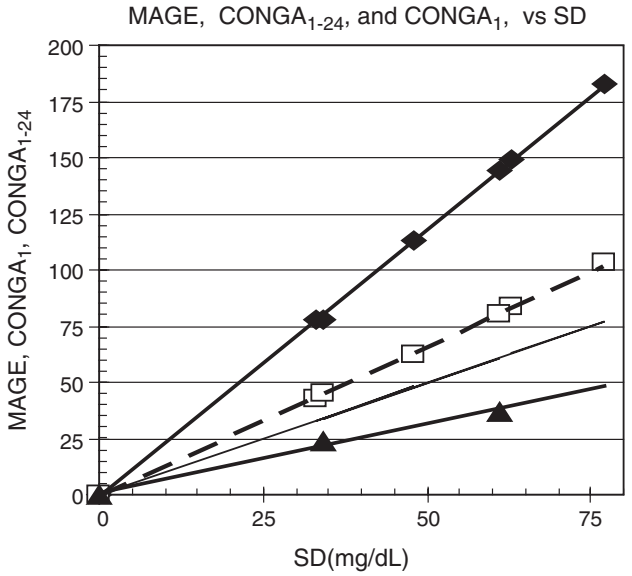

FIG. 1. Relationships among measures of variability within days: MAGE (solid diamonds), $CONGA_{1–24}$ (open squares), SD (line with no symbols), and $CONGA_1$ (solid triangles). Direct linear proportionality between tertiles (33.3^{rd} and 66.7^{th} percentiles) for a large series of patients for the distributions of MAGE, $CONGA_1$, and the average of $CONGA_1$ – $CONGA_{24}$, with tertiles of SD. There would be increased scatter around the best-fitting lines if data for individual subjects were shown. However, the underlying relationships remain the same.

Table 2. Subtypes of SDs

Concept	*Abbreviation*	*Calculation*
Pooling data from all time points and from all days		
Overall (total) SD	SD_T	SD of *all* data from *all days* and *all times of day* ("time points")
Between points in time ("vertical")		
Within days	SD_w	Calculate SD for all measurements in each 24-h day, and then average the SD values
Between time points	$SD_{hh:mm}$	Calculate the average glucose for any time of day for all days; then calculate the SD of this average glycemic profile versus time
Within series	$SD_{ws\ h}$	SD for any desired segment of the glucose series (e.g., $h = 1$ h corresponding to 12 consecutive glucose values obtained at 5-min intervals) calculated at all possible times of day and then averaged. Permits analysis of changes in variability by time of day[a]
Between days ("horizontal")		
Daily means	SD_{dm}	Calculate mean glucose for each day; then calculate SD of these means
Between days—within time points	$SD_{b\ hh:mm}$	Calculate the SD of glucose values for any specified time of day; then calculate the average of these SDs. Permits analysis of changes in variability by time of day[a,b]
Between days—within time points, corrected for changes in daily means	$SD_{b\ hh:mm\ //\ dm}$	As for $SD_{b\ hh:mm}$ calculated above, using the deviations of each observation from the mean for the same day[b]
Interaction: a measure of the variability of glucose profiles on different days	SD_I	Obtained using a two-way analysis of variance with replication[c]

[a]One can plot $SD_{ws\ h}$ versus the midpoint of the time segment for which it was calculated to identify underlying trends of within-day variability by time of day. There will be considerable scatter around this relationship, so that smoothing (e.g., with a running average, polynomial, or smoothing spline) will be necessary to reveal the underlying relationship. One should impose constraints to ensure continuity, so that the predicted value at 11:59:59 p.m. is identical to that at 12:00:00 a.m. The relationship of $CONGA_n$ to time of day can be examined using a similar approach. Variability often decreases overnight when the subject is sleeping and in the absence of food intake, insulin boluses, exercise, and/or stress; such patterns can be revealed by this kind of analysis.

[b]One can plot $SD_{b\ hh:mm}$ or $SD_{b\ hh:mm\ //\ dm}$ versus the time of day for which it was calculated to examine the between-day variability in relation to time of day.

[c]The SD_I is obtained as the square root of the mean square due to interaction of patterns by time of day with sequential days.

previous days, even if the pattern around the mean remained constant. Accordingly, we can adjust all of the glucose values for a given day by subtracting the mean glucose for that day and adding the "grand mean" glucose for the entire data set. If we then calculate the between-day within time point SD, the value will be smaller than $SD_{b\ hh:mm}$, and we designate this as $SD_{b\ hh:mm\ //\ dm}$, indicating that it has been corrected for daily means. Both $SD_{b\ hh:mm}$ and $SD_{b\ hh:mm\ //\ dm}$ can vary by time of day.

The computing format for calculation of these types of SDs is easily implemented using a spreadsheet. We have observed a very high degree of correlation of each of these different types of SD with the overall SD or SD_T and with each other.[18,30]

Measures of glycemic control

In addition to the measures of glycemic variability (Table 1), there are multiple criteria for "quality of glycemic control" (Table 3).

Interrelationship of measures of quality of glycemic control

As in the case of the measures of glycemic variability, we are faced with a multiplicity of measures or indices of *quality* of glycemic control—of which only a few have made their way into routine clinical practice. Some of these have a fairly obscure mathematical formulation that is not intuitively obvious or understandable. Further, it is not clear to what extent these measures are correlated and essentially measuring the same underlying entity, concept, or construct. We have used a combination of empirical data analysis and theoretical analysis to examine these questions.

Empirical analysis. We have calculated a series of these measures for the data of Garg and Jovanovic,[20] including a weighted average of glucose values (M_R) (e.g., M_{100} is calculated using $R = 100$ mg/dL), a measure of quality of glycemic control based on mean and SD (**J**), the Index of Glycemic Control (IGC), the Glycemic Risk Assessment Diabetes Equation (GRADE), and the Average Daily Risk Range (ADRR), and compared them with the percentage of glucose values within a specified range, viz., between 80 and 200 mg/dL.[30]

All six measures are very highly and significantly correlated despite the fact that each of them provides somewhat different weights to hyperglycemic and hypoglycemic values (compare Table 3 and Fig. 2). The correlation coefficients with the percentage of measurements in the range 80–200 mg/dL for M_{100}, GRADE, **J**, IGC, and ADRR were $r = -0.886$, -0.875, -0.848, -0.761, and -0.642, respectively.[30] Similar results were obtained for correlations with percentage of values within other

Table 3. Measures of Quality of Glycemic Control

Criterion	*Definition*	*References*	*Advantages*	*Disadvantages*
1. Percentage in target range	80–200 mg/dL 70–180 mg/dL 70–140 mg/dL	Garg et al.,[19] Garg and Jovanovic,[20] Bailey et al.[21]	Simple, direct, effective (sensitive to interventions)	Arbitrary target range may not be optimal
2. Percentage below target range	<80 mg/dL <50 mg/dL	Garg et al.,[19] Garg and Jovanovic,[20] Bailey et al.[21]	Simple, direct	Does not give more weight to extremely low values
3. Percentage above target range	>250 mg/dL >200 mg/dL >180 mg/dL >140 mg/dL	Garg et al.,[19] Garg and Jovanovic,[20] Bailey et al.[21]	Simple, direct	Does not give more weight to extremely high values
4. Mean glucose (Mean or $Mean_T$)[a]	Mean of all glucose values	Rodbard[4]	Simple, classical; best correlation with A1c[1,4,6,7,16,17]	Does not assign more importance to severe hypoglycemia and hyperglycemia
5. SD (total) (SD or SD_T)[b,c]	SD of all glucose values	Rodbard,[4] Hirsch[5]	Simple, classical statistical method[1,4,6,7]	Combines information on variability from different sources; does not address non-Gaussian skewed asymmetrical distribution or outliers
6. %CV	$=100\times SD_T/Mean_T$		Simple, classical	Subject to same limitations as the SD
7. M_{100} (M_R with $R=100$ mg/dL)	Average of transformed glucose values, using $1{,}000\times \lvert \log_{10}(Glucose/100)\rvert^3$	Schlichtkrull et al.,[22] Wójcicki[23]	Assigns more importance to hypoglycemia than to hyperglycemia; highly correlated with percentage of time in target range[30]	Fails to provide enough weight to hypoglycemic values
8. MAGE	Average amplitude of upstrokes or downstrokes with magnitude greater than 1 SD	Service et al.,[10,12] Service and Nelson[11]	Attempts to describe major fluctuations, e.g., due to meals. Directly proportional to and highly correlated with SD of all glucose values, SD_T (Fig. 1)	Rarely used. Less efficient statistically than SD_T
9A. MODD	Mean difference between glucose values obtained at the same time of day on two consecutive days under standardized conditions	Service and Nelson,[11] Service et al.[12]	Describes *between-day* variability. Directly proportional to and highly correlated with SD of all glucose values, SD_T (Fig. 1)	Originally only defined for two consecutive days assuming similar meals, activities, and therapy on both days
9B. $MODD_d$	Mean of differences in glucose between each value and the value exactly $d\times 24$ hours later, calculated for each observation in a time series where data are available	This report and Rodbard et al.[18, 30]	Extends MODD to permit use of data from multiple days; agrees well with average of MODD from multiple days	New
10. **J**	Combination of information from mean and SD of all glucose values $=0.001\times(mean+SD)^2$	Wójcicki[24]	Combines mean and SD; highly correlated with percentage of time in target range[30]	Rarely used; sensitive to hyperglycemia but relatively insensitive to hypoglycemia
11. Index of Glycemic Control (IGC) or Figure of Merit (FOM)	Sum of Hyperglycemia Index and Hypoglycemia Index	cf. Appendix 2, Rodbard,[18,25] Rodbard et al.[30]	Adjustable weighting of hypo- and hyperglycemia and for extreme values; can mimic LBGI, HBGI, or GRADE; relatively simple and understandable mathematically; highly correlated with percentage of time in target range[30]	Relatively new; unfamiliar

12. Hyperglycemia Index parameters: $ULTR = 140$ mg/dL, $a = 1.1$, $c = 30$	Weighted average of hyperglycemic values, e.g., $(\text{Glucose} - 140)^{1.1}/30$	cf. Appendix 2, Rodbard,[18,25] Rodbard et al.[30]	Adjusts weights for mild, moderate, or severe hyperglycemia; relatively simple mathematically	Relatively new; unfamiliar
13. Hypoglycemia Index parameters: $LLTR = 80$ mg/dL, $b = 2.0$, $d = 30$	Weighted average of hypoglycemic values (glucose < LLTR), e.g., $(80 - \text{Glucose})^{2.0}/30$	cf. Appendix 2, Rodbard,[18,25] Rodbard et al.[30]	Adjusts weights for mild, moderate, or severe hypoglycemia; relatively simple mathematically	Relatively new; unfamiliar
14. Average Daily Risk Range (ADRR)	Average sum of |HBGI for maximum glucose| plus |LBGI for minimum glucose| for each day	Kovatchev et al.[26–28]	Combines information from HBGI and LBGI; moderate correlation with percentage of time in target range for SMBG	Calculated using extreme values (MIN, MAX); more appropriate for SMBG than for CGM data. For SMBG, requires 30 days with at least four values per day. Currently unclear how best to apply to CGM[d]
15. Low Blood Glucose Index (LBGI)	For glucose values <112.5 mg/dL average of $27.695 \times (\log_e(\text{Glucose})^{1.084} - 5.381)$	Kovatchev et al.[26–28]	Heavier weights assigned to severe hypoglycemic values	Obscure mathematical form
16. High Blood Glucose Index (HBGI)	For glucose values >112.5 mg/dL, average of $27.695 \times (\log_e(\text{Glucose})^{1.084} - 5.381)$	Kovatchev et al.[26–28]	Heavier weights assigned to severe hyperglycemic values	Obscure mathematical form
17. Glycemic Risk Assessment Diabetes Equation (GRADE)	Average of transformed glucose values[e] = Min[50, $42.5 \times \{\log_{10}(\log_{10}(\text{Glucose}/18) + 0.16)^2)\}$]	Hill et al.[29]	Based on clinicians' value judgments of relative import of hypo- and hyperglycemia; highly correlated with percentage of time in target range[30]	New; rarely used; may not provide sufficient weight to the hypoglycemic range. Obscure mathematical form.
18. $\%GRADE_{hyperglycemia}$	Percentage of GRADE score attributable to glucose values above 140 mg/dL	Hill et al.[29]	Measure of relative importance of hyperglycemia	New; unfamiliar
19. $\%GRADE_{hypoglycemia}$	Percentage of GRADE score attributable to glucose values below 70 mg/dL	Hill et al.[29]	Measure of relative importance of hypoglycemia	New; unfamiliar
20. $\%GRADE_{euglycemia}$	Percentage of GRADE score attributable to glucose values within the range 70–140 mg/dL	Hill et al.[29]	Weighted measure of percentage of values within target range; emphasizes borderline hypo- and hyperglycemia; reflects percentage in the range 70–140 mg/dL	New; unfamiliar; includes effects of both borderline low and borderline high values

[a]Alternatively, one can use the 50th percentile (the median) with nearly identical results in the case of CGM data.[4,7–9]

[b]Alternatively, one can use the IQR, where IQR = 75th percentile − 25th percentile, or one can estimate the SD based on the IQR, with nearly identical results in the case of CGM data.[4,7–9] For CGM data there is little advantage to use of IQR relative to SD.

[c]One can test for Gaussianness of the glucose distribution and apply various transformations to improve Gaussianness, thereby improving the informativeness of the SD and avoiding potential problems due to the frequent presence of positive skewness (asymmetry) of the distribution.

[d]For SMBG, requires 30 days, a minimum of 75 values, and four values on a given day for that day to be included in the average. Requirements for CGM data have not been specified.[28]

[e]This formula corrects a typographical error in the original report of Hill et al.[29] for the case when glucose is expressed in units of mg/dL.

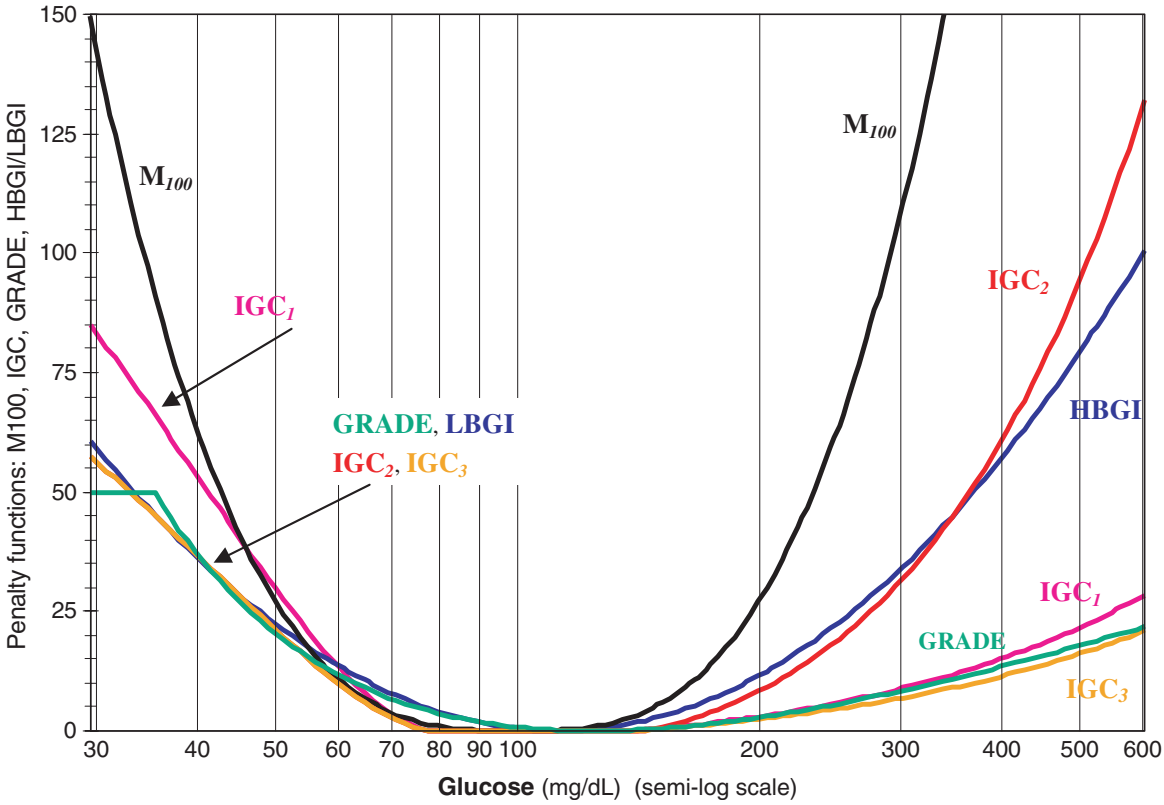

FIG. 2. Relationship of penalty functions (ordinate) to glucose level (mg/dL) on semi-log scale (abscissa). $\mathbf{M_{100}}$: black; $\mathbf{IGC_1}$: pink; **HBGI** and **LBGI**: blue; **GRADE**: green; $\mathbf{IGC_2}$: red; $\mathbf{IGC_3}$: light orange. $\mathbf{IGC_2}$ is nearly identical to **HGBI** and **LBGI**; $\mathbf{IGC_3}$ is nearly identical to **GRADE**. Parameters for the three cases for **IGC**: **LLTR** = 80; **ULTR** = 140, $\boldsymbol{c} = \boldsymbol{d} = 30$; $\mathbf{IGC_1}$: $\boldsymbol{a} = 1.1$, $\boldsymbol{b} = 2.0$; $\mathbf{IGC_2}$: $\boldsymbol{a} = 1.35$, $\boldsymbol{b} = 1.9$; $\mathbf{IGC_3}$: $\boldsymbol{a} = 1.05$, $\boldsymbol{b} = 1.9$. $\mathbf{M_{100}}$, **HBGI, LBGI** and **GRADE** are defined in Table 3; **IGC** is defined in Table 3 and in Appendix 2.

target ranges, e.g., 70–180 mg/dL and 80–150 mg/dL, and for data from two additional 1-week periods and from a 2-week period. The correlation coefficients indicated that there was a very high degree of consensus among five criteria: M_{100}, GRADE, **J**, IGC, and percentage in range 80–200 mg/dL.

Theoretical analysis. One can predict the extent of correlation of results using several indices by analysis of the mathematical definitions of those indices. Using the mathematical definitions of M_{100}, IGC, Low Blood Glucose Index (LBGI) and High Blood Glucose Index (HBGI), and GRADE,[22,25–29] one can evaluate how each of these indices "maps" or transforms glucose values into a "score" (Fig. 2). These methods assign an increased weight or importance to hypoglycemic values relative to hyperglycemic values, and also provide greater weight on values that fall progressively outside the target range.

The IGC, Hyperglycemia Index, Hypoglycemia Index, HBGI and LBGI, and GRADE assign larger penalties to the hypoglycemic range than does the original Schlichtkrull M_R. The IGC can be set up with coefficients (lower limit of target range [*LLTR*], upper limit of target range [*ULTR*], expontents *a*, *b*, scaling factors *c*, *d*) so as to make it nearly identical to the combination of HBGI and LBGI or to the GRADE score.

The Schlichtkrull M_{100} value is symmetrical with respect to the log scale for glucose (Fig. 2), whereas the other methods assign greater importance and influence to hypoglycemic values than to the hyperglycemic values even when glucose is displayed on a semi-log scale. For example, M_{100} assigns equal importance to 50 and to 200 mg/dL, which appears to provide too little weight or importance to a severely hypoglycemic value. In contrast, the IGC (using the originally proposed parameters) assigns equal importance to 50 and 625 mg/dL, the combination of LBGI and HBGI assigns equal importance to 50 and to 250 mg/dL, and the GRADE score of Hill et al.[29] assigns equal importance to 50 mg/dL and to 215 mg/dL. The IGC has the advantage of flexibility: its parameters can be adjusted so that it can mimic either the GRADE score or the combination of LBGI and HBGI.

It is generally desirable to set two of the six parameters in the definition of the IGC to a constant, i.e., $c = d = 30$, so that the range of numerical values is close to those for M_{100}, LBGI, HBGI, and GRADE (Fig. 3). If desired, *LLTR* and *ULTR* could be set equal to each other (e.g., $LLTR = ULTR = 112.5$ mg/dL), reducing the number of parameters to three. The LBGI and HBGI utilize three numerical parameters (a target glucose value of 112.5 mg/dL, the exponent 1.084, and the constant 5.381 (criteria 15 and 16 in Table 3), while the GRADE Score uses two numerical parameters (the constants 42.5 and 0.16 in criterion 17 in Table 3). Compared with IGC_1, IGC_2 gives greater weight to hyperglycemic values and lower weight to hypoglycemic values. IGC_3 gives the same weight to hypoglycemic values as does IGC_2, but less weight to hyperglycemic values (Fig. 2).

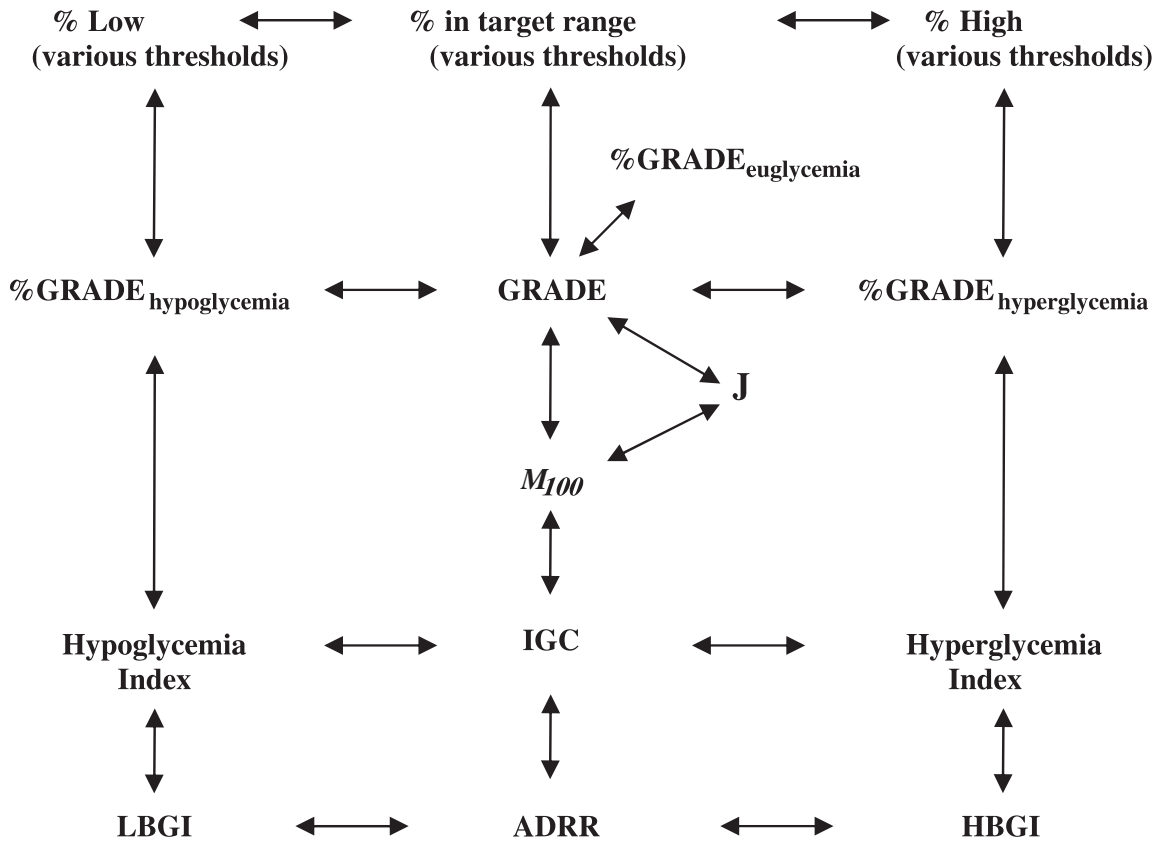

FIG. 3. Relationships among criteria for quality of glycemic control and glycemic variability.

Discussion

Interrelationships of several measures of glycemic control

Several of the major interrelationships among measures of glycemic control are shown in Figure 3. These measures can be grouped to indicate whether they are predominantly assessing hypoglycemia (e.g., percentage below 50 mg/dL, Hypoglycemia Index, LBGI, $\%GRADE_{hypoglycemia}$), hyperglycemia (e.g., percentage above 250 mg/dL, Hyperglycemia Index, HBGI, $\%GRADE_{hyperglycemia}$), euglycemia (e.g., percentage between 80 and 140 mg/dL, $\%GRADE_{euglycemia}$), or a combination of all three facets of glycemic control (e.g., M_{100}, IGC, GRADE, ADRR). For some representative data,[18–21,30] we observed a high degree of correlation for the GRADE score, IGC, M_{100}, and the **J** index with the percentage of glucose values in the range 80–200 mg/dL. This concordance indicates that these parameters are generally measuring the same "construct" or conceptual entity. However, the extent of these correlations is likely to depend on whether one is dealing with data sets involving predominantly hyper- or hypoglycemia and may vary somewhat between patients or groups of patients.

Similarly, we can evaluate the correlations of each of the several measures of glycemic *variability*. All of the measures are highly correlated with the overall SD, SD_T. It is helpful to keep in mind the different "families" of measures of variability, i.e., measuring *within-day* variability or *between-day* variability. As indicated in Table 2, there are seven different types or subtypes of SD. It is fairly easy to compute each of these measures and to evaluate which of them has changed in response to a therapeutic intervention within a given individual or which indices of variability are significantly different in different patient groups.

MAGE. It is likely that most users of MAGE utilized a graphical approach to its estimation. The original definition did not give sufficient detail to enable one to develop an unambiguous computing algorithm.[10–12] First, MAGE utilizes a criterion that a deflection (upstroke or downstroke) must be at least equal to the SD. Is the SD to be calculated separately for each day, or for an entire multiday series (e.g., SD_T)? Should one use the same SD to evaluate excursions on different days, or use the SD derived on data from only that one day? Second, there is a potential problem with the discontinuity that occurs as one "clicks over" from one day to another because either an upstroke or downstroke can potentially extend from one day to the next. Third, there is an element of chance: the MAGE uses data from either upstrokes or downstrokes, depending on whether an upstroke or downstroke is identified first. This introduces a random chance event, which depends on the time of day for the initiation of the series. There can be loss of information by not using both the upstrokes or downstrokes. Fourth, and most importantly, there can be ambiguity as to where an upstroke (or downstroke) begins and ends. If an upstroke satisfies the "1 SD" criterion but then declines slightly followed by another upswing, there will be ambiguity as to where the peak ends, and hence in the magnitude

(amplitude) of the excursion. Similar problems arise with downstrokes. These problems become more severe as the frequency of glucose measurements increases but are ameliorated if one smoothes the curve (of glucose vs. time) before the analysis is performed. There is need for empirical studies to evaluate which method of calculation of MAGE is best in terms of its precision, reproducibility, and ability to detect changes in clinical studies of responses to therapeutic interventions. It is possible that computer programs to calculate MAGE used by different investigators might give discrepant results if applied to a specified (reference) dataset. Hence, there is need for a standardized or "gold standard" algorithm and computer program. Further, given the very high correlation of MAGE and the overall SD (Fig. 1), it may not be necessary to use the MAGE at all: SD_T may be superior in terms of its definition, ease of computation, precision (sampling error), and reproducibility between replicated time periods (e.g., different weeks).

MODD. The MODD was originally measured using a rigorous protocol involving two consecutive days with the subject in a clinical research center with standardized meals, mealtimes, exercise, and therapy. There is some question as to the best method to calculate this index when we have several days of data as is generally the case when data are obtained using CGM. We have utilized a method of computation, $MODD_d$, that allows us to calculate the MODD for a continuous time series involving many days. The new method of calculation shows a very high correlation (e.g., $r = 0.96$ for $d = 1$) with the implicit original method (averaging MODD for all pairs of consecutive days). $MODD_1$ is also almost perfectly correlated with $CONGA_{24}$ (as expected from their definitions) and shows a high degree of correlation with SD_{dm}, $SD_{b\ hh:mm}$, $SD_{b\ hh:mm\ //\ dm}$, and SD_T. It remains to be seen which index proves to be the most informative in terms of monitoring patients or conducting clinical research.

$CONGA_n$. $CONGA_n$ appears to be a promising measure of glycemic variability.[15] The value for $CONGA_n$ varies systematically with the value of n, i.e., the size of the "window" or duration of the time segment used to compute the variability. It remains to be seen whether $CONGA_n$ or $SD_{ws\ h}$ provides a better, more reproducible, and sensitive measure of changes in short-term variability. Our initial studies of $CONGA_n$ and $SD_{ws\ h}$ indicate that these measures can increase in response to an intervention when we use some values of n (or h) but decrease when using other values of n or h. The n value for $CONGA_n$ and the h for $SD_{ws\ h}$ are not equivalent: $CONGA_2$ has a higher correlation with $SD_{ws\ 4}$ than with $SD_{ws\ 2}$. In general, it appears that $CONGA_n$ has its highest correlation with $SD_{ws\ h}$ when $h \sim 2.5n$. (Note that $CONGA_n$ measures the variability at exactly n hours of separation of glucose values, whereas $SD_{ws\ h}$ measures the variability at h hours of separation combined with variability within all shorter time segments, so that the effective width of the "time window" is approximately $\sim h/2$.)

IGC. The IGC has adjustable parameters and can be "tuned" to give nearly perfect concordance with GRADE or LBGI and HBGI (Fig. 2). The IGC has the potential advantage that it can also be tuned to provide more influence to the severely hypoglycemic ranges, and this can make it more sensitive than the other measures when dealing predominantly with problems of hypoglycemia.

ADRR. Despite the fact that the underlying LBGI and HBGI are very closely related to GRADE, M_{100}, and IGC (Fig. 2), ADRR shows a relatively weak correlation with percentage of glucose values within the range 80–200 mg/dL ($r = -0.642$).[30] ADRR was also relatively insensitive to a therapeutic intervention, the unmasking of the CGM data to provide real-time feedback to patients.[30] We believe that this may be due in large part to the use of the maximum (MAX) and minimum (MIN) glucose values for any given 24-h period in the definition of ADRR. Use of MAX and MIN may be effective when dealing with the small number (e.g., two to 10) of daily glucose values typically obtained using self-monitoring of blood glucose, but not for the massive number of values (e.g., >200) obtained daily using CGM. With such a large number of observations, it becomes highly probable that the MIN and MAX will approach the lower and upper limits of the measurement scale [e.g., 40 and 400 mg/dL] such that the ADRR will lose much of its ability to discriminate between different days. Accordingly, the ADRR might become more sensitive if it were to use the 10^{th} and 90^{th} percentiles for glucose values, rather than the MIN and MAX. Alternatively, one could use an approach similar to that used for the IGC[18, 25] and GRADE,[29] i.e., using an average of the HBGI/LBGI-transformed glucose values, thereby utilizing information from all of the glucose values rather than just two (MIN and MAX).

New measures of SD. In the present report we propose the use of several new measures of subtypes of SDs (SD_T, SD_w, $SD_{hh:mm}$, $SD_{ws\ h}$, SD_{dm}, $SD_{b\ hh:mm}$, $SD_{b\ hh:mm\ //\ dm}$, and SD_I). It remains to be seen how useful each of these may be in clinical practice. Under many conditions, each of these subtypes of SD is highly correlated with the overall SD or SD_T. However, when one introduces new treatments or other interventions, these parameters can show distinctive patterns of changes, with some parameters increasing and others decreasing.[30] For example, $SD_{ws\ h}$ might increase for $h = 1$ to 4, but decrease for $h = 8$, 12, or 24.[30] These kinds of observations can be useful to quantify changes in different characteristics of patterns in the glycemic profile (e.g., increasing rapid or high frequency fluctuations, but decreasing slow or low frequency fluctuations, as might be reflected in a periodogram). At present one must use an empirical approach to evaluate which set of parameters is most useful for addressing any particular clinical or research question.

When a patient shows a substantial amount of glycemic variability, there is variability in nearly all aspects—within days, within short time periods, between daily means, and between days–within time points. Accordingly, when we need a simple measure to characterize variability, one of the best overall measures is likely to be the overall SD, SD_T. However, the percentage of values within a specified range (e.g., 80–200 mg/dL) can be as effective or even more effective in detecting changes in response to interventions.[30]

A practical approach

Clinical investigators and clinicians may find it useful to employ a systematic approach to analysis and interpretation of CGM data such as the one summarized in Scheme 1.

SCHEME 1. A systematic approach to analysis of CGM data.

Questions to be addressed:

1. **Quantity and quality of the data**
   - a. Is there sufficient quantity of data?
     - i. Number of days?
     - ii. Amount of missing data?
     - iii. Amount of data deemed unreliable due to instability or inadequate calibration?
   - b. Are the data of sufficient quality?
     - i. Correlation with self-monitoring of blood glucose
     - ii. Frequency of calibration
     - iii. Correlation with clinical events (e.g., hypoglycemia)
     - iv. Magnitude of short-term variability in the data
2. **What is the overall mean glucose?**
   - a. Is this consistent with the recently measured values for A1c?[17]
   - b. Is this consistent with the recently available data from self-monitoring of blood glucose?
     - i. Mean, SD, patterns
3. **What is the overall variability as measured by the SD (SD_T) for all of the data, expressed both in absolute terms and as a percentage of the overall mean (%CV)?**
   - a. If data are available, how do these values compare with data from previous periods?
4. **Hypoglycemia: frequency, severity, dates, time of day**
   - a. % of values below specified targets (e.g. 50, 80 mg/dL)
   - b. Number of hypoglycemia events
   - c. Severity of hypoglycemia events
5. **Hyperglycemia: frequency, severity, dates, time of day**
   - a. % of values above specified targets (e.g. 180, 250 mg/dL)
   - b. Number of hyperglycemia events
   - c. Severity of hyperglycemia events
6. **What kinds of patterns are evident on graphical display of the data?**
   - a. Glucose versus date (high-resolution graphical display)
     - i. Average level, extent of scatter, longitudinal trends
     - ii. Are there periods of time that appear to have a different mean, scatter, or pattern?
       1. If so, can this be correlated with intercurrent events such as illness, travel, medications, or lifestyle changes?
   - b. Glucose versus time of day (high-resolution graphical display of "Glucose Profile" showing 10^{th}, 25^{th}, 50^{th}, 75^{th}, and 90^{th} percentiles (smoothed) superimposed on the original data points)
     - i. Average level, extent of scatter
     - ii. Is there a consistent pattern from day to day?
       1. If not, is the variation between days due to:
          - a. Different overall mean level for that day?
          - b. Different magnitude of postprandial excursions?
          - c. Different timing of postprandial excursions?
          - d. Changes in patterns overnight?
     - iii. Are postprandial peaks evident?
       1. Is there a consistent pattern for postprandial glucose following breakfast? lunch? dinner?
     - iv. Times of day when hypoglycemia is most common
       1. Severity and duration of the hypoglycemia
     - v. Times of day when hyperglycemia is most prevalent
       1. Severity and duration of the hyperglycemia
     - vi. Identification of days with unusual patterns
       1. Possible rebound or overtreatment of hypoglycemia
       2. Possible overtreatment of hyperglycemia
   - c. Glucose in relationship to day of the week (if data are available for 1 month or longer)
     - i. Does the average, scatter, or pattern (profile) depend on day of the week?
7. **Interpretation of indices of overall quality of glycemic control**
   - a. Schlichtkrull M_{100} value (reference level 100 mg/dL)
   - b. **J** Index[24]
   - c. Index of Glycemic Control[25] (see Appendix) and corresponding Hypoglycemia Index and Hyperglycemia Index
   - d. LBGI, HBGI, ADRR[26–28]
   - e. GRADE score[29]
   - f. Interpretation of each of the above in terms of:
     - i. Change since previous periods for the same patient
     - ii. Percentiles for a reference group of subjects matched by

SCHEME 1. Continued.

1. Type of diabetes (type 1, type 2)
2. Duration of diabetes
3. Therapeutic regimen

g. Graphical display of these indices
   i. Comment: it is assumed that each physician will develop experience with one or more of these indices and select the one or ones that he/she prefers

8. Detailed analysis of variability:

a. Quantitative characterization of variability in terms of its components:
   i. Total variability, SD_T
   ii. Variability between times of day
      1. Variability within days: SD_w, MAGE
      2. Variability in the average pattern by time of day (as averaged over all days in the time period being analyzed): $SD_{hh:mm}$
         a. Assessment of the stability/reproducibility of the patterns by time of day[18,30]
            i. ($SD_{hh:mm}/SD_w$), SD_I
            ii. Ability to predict glucose at any given time of day, given the mean value for that time of day, for all days considered jointly
      3. Variability within short time segments (e.g., 1 hour): $SD_{ws\ h}$, for $h = 1$, $CONGA_n$, for $n = 1$
   iii. Variability between days
      1. Variability between different days—at the same time points: $SD_{b\ hh:mm}$, MODD, $MODD_1$, $CONGA_{24}$
      2. Variability between days, within time points, after correction for changes in the daily mean: $SD_{b\ hh:mm\ //\ dm}$
   iv. Identification of the components of variability that appear to be most important for management of any particular patient

b. Further analyses:
   i. Does local "within series" variability depend on time of day? (Examine smoothed curve of $SD_{ws\ h}$ vs. time of day)
   ii. Does between day–within time point variability depend on time of day? (Examine smoothed curve of $SD_{b\ hh:mm}$ vs. time of day)

It would be desirable to incorporate many of these types of analysis as options into commercially available programs for routine retrospective interpretation of CGM data. It will be essential to optimize the usability and "user friendliness" of the programs so that clinicians and clinical investigators can understand the displays and utilize the information effectively. All of these analyses can be performed automatically by the program, and the results presented in a prespecified order of priority. It remains to be seen which of these multiple parameters will be embraced by the clinical investigator and clinical practitioner.

In view of the multiple types of indices available, the clinical investigator and clinician may wish to focus on a select few. Based on the above discussion, we would recommend the following parameters as measures of overall quality of glycemic control: A1c, mean glucose ($Mean_T$), and IGC or GRADE. Likewise, we would recommend the following as the principal indices of glycemic variability: SD_T, SD_w, or MAGE, as a measure of within-day variability, and $SD_{b\ hh:mm}$, or MODD, as a measure of between-day variability. Additional measures may be needed in certain studies or for some purposes in specific patients.

Conclusions

Many indices have been proposed to measure glycemic variability and quality of glycemic control. Most of these indices are highly correlated, and, accordingly, they convey largely the same information, making it possible to reduce the number of indices that one needs to consider. The overall SD, SD_T, is highly correlated with other measures of variability, e.g., IQR, MAGE, MODD, and $CONGA_n$, and with the other types or subtypes of SD (SD_w, $SD_{hh:mm}$, $SD_{ws\ h}$, SD_{dm}, $SD_{b\ hh:mm}$, and $SD_{b\ hh:mm\ //\ dm}$). The individual components of variability (e.g., within days, between days) are highly correlated with the overall SD but enable one to identify a series of specific types of problems or changes in glycemic profiles in response to therapeutic interventions. Variability, as measured by $SD_{ws\ h}$, $CONGA_n$, $SD_{b\ hh:mm}$, or $SD_{b\ hh:mm\ //\ dm}$, can vary systematically by time of day. Four measures of quality of glycemic control (M_{100}, IGC, GRADE, and HBGI/LBGI) are also highly correlated among themselves as predicted theoretically (Fig. 2) and as shown empirically[30]: the percentage of glucose observations within a specified range (e.g., 80–200 mg/dL) is highly correlated with M_{100}, **J**, IGC, and GRADE and has high sensitivity for detection of changes in response to some interventions (e.g., unmasking of CGM data). We have suggested modifications to improve the calculation of MAGE, MODD, and ADRR. We show the relationships among these measures schematically (Fig. 3). These results provide a foundation for a systematic approach to the interpretation of CGM data that will be useful to both the clinical investigator and clinician. We make recommendations for selection of a minimal size set of parameters.

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(Appendix 1 and 2 follow →)

Appendix 1

Symbol	*Definition*	*References*
a, *b*, *c*, *d*	Constants, used in calculating IGC	18, 25, 30
ADRR	Average Daily Risk Range	28
AGP	Ambulatory glucose profile	8, 9
$CONGA_n$	Measure of within-day glucose variability: SD of differences between any glucose value and another one exactly *n* hours later. Mnemonic: "Continuous Overlapping Net Glycemic Action"	15
$CONGA_{1–24}$	Average of $CONGA_1$ through $CONGA_{24}$; provides an overall measures of variability within days	16, 17
%CV	% coefficient of variation = 100×SD/mean	4–9
GRADE	Weighted average of glucose values, giving a greater penalties to hypoglycemia than hyperglycemia, and to more severe departures from the target level of 105 mg/dL. Mnemonic: "Glycemic Risk Assessment Diabetes Equation"	29
$\%GRADE_{hyperglycemia}$	% of GRADE score attributable to values below 70 mg/dL	29
$\%GRADE_{euglycemia}$	% of GRADE score attributable to values between 70 and 140 mg/dL	29
$\%GRADE_{hypoglycemia}$	% of GRADE score attributable to values above 140 mg/dL	29
HBGI	High Blood Glucose Index	26, 28
Hyperglycemia Index	Weighted average of hyperglycemic values, with larger penalties for more extreme values	18, 25, 30
Hypoglycemia Index	Weighted average of hypoglycemic values, with progressively larger penalties for more extreme values	18, 25, 30
HYPO	A measure of hypoglycemia	13,14
IGC	Index of Glycemic Control (previously designated "Figure of Merit"); sum of Hypoglycemia Index and Hyperglycemia Index	18, 25, 30
IQR	Inter-Quartile Range	4, 6–9
J	Measure of quality of glycemic control based on mean and SD: $\mathbf{J} = 0.001 \times (\text{mean} + \text{SD})^2$	24
LBGI	Low Blood Glucose Index	26, 28
LI	Lability Index	13, 14
LLTR	Lower limit of the target range, e.g., 80 mg/dL	18, 25
$Mean_T$	Mean of all glucose values (multiple times of day, multiple days)	18, 25, 30
M_R, M_{100}	Weighted average of glucose values, with progressively larger penalties for more extreme values ($M_{100} = M$ with reference value $R = 100$ mg/dL)	22
MAGE	Mean amplitude of glycemic excursions	10, 12
MODD	Mean of daily differences	11, 12
$MODD_d$	MODD calculated as the mean absolute difference of glucose values separated by exactly 24×*d* hours	11, 18
r	Correlation coefficient	
R	Reference value for Schlichtkrull's M_R, e.g., $R = 100$ mg/dL	22
SD	Standard deviation (generic)	4–9
$SD_{b\ hh:mm}$	SD between days, within time points	18
$SD_{b\ hh:mm\ //\ dm}$	SD between days, within time points, corrected for changes in daily means	18
SD_{dm}	SD of daily mean glucose	18
$SD_{hh:mm}$	SD between time points (designated as *hh:mm*), for mean glucose values from several days	18
SD_T	"Total" SD	18
SD_w	SD within days	18
$SD_{ws\ h}$	SD within series, for a span of *h* hours	18
ULTR	Upper limit of the target range, e.g., 140 mg/dL	18, 25

Appendix 2. Definitions of Index of Glycemic Control (IGC), Hypoglycemia Index, and Hyperglycemia Index

$$\textbf{IGC} = \textbf{Hypoglycemia Index} + \textbf{Hyperglycemia Index} \quad \text{(equation A.1)}$$

Hypoglycemia Index:
Definitions of parameters:
Glucose values are expressed as mg/dL.
LLTR = **L**ower **L**imit of **T**arget **R**ange, with default value of **80** mg/dL
b = exponent, generally in the range from 1.0 to 2.0, with default value of **2.0**.
d = scaling factor to permit another form of differential weighting of hypoglycemic and hyperglycemic values; The default value, $d = 30$, was selected to display the Hypoglycemia Index, Hyperglycemic Index and IGC on approximately the same range of numerical values as HBGI/LBGI and GRADE

$$\textbf{Hypoglycemic Index} = \left\{\Sigma(\textbf{LLTR} - \text{Glucose})^{b}\right\}/[\text{N} \times d] \quad \text{(equation A.2)}$$

The summation is performed for glucose values less than **LLTR**, excluding any missing observations. N is the total number of observations, including hypo-, eu-, and hyperglycemic values. The scaling factor d is given a default value of 30, but could be used to differentially weight hypo- and hyperglycemic values.

Hyperglycemic Index:
Definitions of parameters:
Glucose values are expressed as mg/dL.
ULTR = **U**pper **L**imit of **T**arget **R**ange, with default value of **140** mg/dL;
a = exponent, generally in the range from 1.0 to 2.0, with default value of **1.1**;
c = scaling factor with a default value, $c = 30$, selected so as to display Hyperglycemia Index, Hypoglycemia Index, and IGC on approximately the same numerical range as measurements of HBGI, LBGI and GRADE. Use of c and d as two distinct adjustable parameters would provide yet another form of differential weighting of the Hypoglycemic and Hyperglycemic Indices, in addition to a and b.

$$\textbf{Hyperglycemia index} = \left\{\Sigma(\text{Glucose} - \textbf{ULTR})^{a}\right\}/[\text{N} \times c] \quad \text{(equation A.3)}$$

The summation is performed for glucose values greater than the **ULTR**, excluding any missing observations. N is the total number of observations, including hypo-, eu-, and hyperglycemic values.
By adjusting the parameters (**ULTR, LLTR,** a, b, c, d) IGC can closely approximate the "penalty function" corresponding to the use of GRADE or the use of HBGI and LBGI.
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