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ORIGINAL ARTICLE

Glucose Variability: A Review of Clinical Applications and Research Developments

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Abstract

Glycemic variability (GV) is a major consideration when evaluating quality of glycemic control. GV increases progressively from prediabetes through advanced T2D and is still higher in T1D. GV is correlated with risk of hypoglycemia. The most popular metrics for GV are the %Coefficient of Variation (%CV) and standard deviation (SD). The %CV is correlated with risk of hypoglycemia. Graphical display of glucose by date, time of day, and day of the week, and display of simplified glucose distributions showing % of time in several ranges, provide clinically useful indicators of GV. SD is highly correlated with most other measures of GV, including interquartile range, mean amplitude of glycemic excursion, mean of daily differences, and average daily risk range. Some metrics are sensitive to the frequency, periodicity, and complexity of glycemic fluctuations, including Fourier analysis, periodograms, frequency spectrum, multiscale entropy (MSE), and Glucose Variability Percentage (GVP). Fourier analysis indicates progressive changes from normal subjects to children and adults with T1D, and from prediabetes to T2D. The GVP identifies novel characteristics for children, adolescents, and adults with type 1 diabetes and for adults with type 2. GVP also demonstrated small rapid glycemic fluctuations in people with T1D when using a dual-hormone closed-loop control. MSE demonstrated systematic changes from normal subjects to people with T2D at various stages of duration, intensity of therapy, and quality of glycemic control. We describe new metrics to characterize postprandial excursions, day-to-day stability of glucose patterns, and systematic changes of patterns by day of the week. Metrics for GV should be interpreted in terms of percentiles and z-scores relative to identified reference populations. There is a need for large accessible databases for reference populations to provide a basis for automated interpretation of GV and other features of continuous glucose monitoring records.

Keywords: Glycemic variability, Hypoglycemia, Hyperglycemia, Ambulatory glucose profile, Continuous glucose monitoring, Time series analysis.

Introduction

Several reviews[1–5] and consensus statements[6–9] are available regarding glycemic variability (GV). In the present report, we will consider selected topics in detail:

(1) clinical, methodological, and statistical issues with respect to characterization of GV;
(2) graphical methods, including several proposed enhancements to the Ambulatory Glucose Profile (AGP)
(3) review of recent findings demonstrating low-amplitude, low-energy rapid oscillations of glucose levels in normal subjects, with progressive loss in people with prediabetes, type 2, and type 1 diabetes.

Multiple metrics for glycemic variability

Dozens of metrics for variability have been proposed.[1–5,10–29] Table 1 displays some of the more important and frequently used metrics.

The standard deviation (SD) can be calculated many different ways for different subsets of the data, reflecting variability on different timescales. These include total variability, SD_T (total variability for a multiday glucose time series reflecting both within and between-day variability), within-day variability (SD_w), variability of the average pattern by time of day (SD of hourly median glucose by time of day ($SD_{hh:mm}$)) when pooling data from multiple days, variability within specified time periods or segments (e.g., before or after meals, at bedtime, overnight), or any segment of *h* hours starting at a

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Table 1. Metrics to Characterize Glycemic Variability

Methods to characterize glycemic variability
1. SD (for various subsets of data, within-days, between-days)
2. %CV (SD expressed as a percentage of the mean)
3. Simplified frequency distribution (% of glucose values within target ranges, % in hypoglycemic ranges, % in hyperglycemic ranges, and other ranges as desired)
4. Glucose frequency distribution and cumulative frequency distribution
5. AGP (smoothed glucose percentiles by time of day)
6. MAGE, MODD, ADRR, $CONGA_n$, $CONGA_{24}$, IQR, MAD
7. GVP, MAG, DT
8. Time series analysis (Fourier analysis, periodogram, spectral frequency density, Multiscale Entropy (MSE), Complexity analysis)

ADRR, Average Daily Risk Range; AGP, Ambulatory Glucose Profile; %CV, %Coefficient of Variation; DT, Distance Traveled; IQR, Inter-Quartile Range; MAD, Mean Absolute Deviation; MAG, Mean Absolute Glucose change per unit time; MAGE, Mean Amplitude of Glycemic Excursion; MODD, Mean Of Daily Differences; SD, Standard Deviation.

specified time (*hh:mm*), ($SD_{ws\ h\ hh:mm}$), variability between daily means (SD_{dm}), and variability between days at exactly the same time each day, (SD_b), between days at the same time of day after correction for the changes in daily means ($SD_{b//dm}$), and variability between days of the week.[1,11,12] These types of variability can be estimated using SD with a customized analysis of variance.[11,12] One could also use metrics, such as Inter-Quartile Range (IQR), %Coefficient of Variation (%CV), or mean absolute deviation[29] to characterize variability on these different timescales.

High correlations among several metrics of glycemic variability

There are high correlations among many of these parameters,[26,30–33] and several theory-based mathematical relationships among them.[11,12] For example, IQR is proportional to SD; mean of daily differences (MODD), SD_b, and $CONGA_{24}$ are directly proportional to each other. Empirically, based on multiple datasets, mean amplitude of glycemic excursion (MAGE) is directly proportional to SD under nearly all circumstances, with MAGE $\sim$2.3 SD, aside from minor random errors.[11,12] Thus, one can restrict attention to only a few metrics without major loss of information. It remains to be seen whether use of a linear combination of parameters, or of a weighted average of parameters, would be significantly more informative and clinically useful than use of a small number of metrics.[30–31,34]

Popular methods

One must distinguish between measures of GV per se, quality of glycemic control (% in target range, M_{100}, Blood Glucose Risk Index (BGRI), Glycemic Risk Assessment Diabetes Equation (GRADE), Index of Glycemic Control (IGC), measures of hypoglycemia (% in hypoglycemic range, Low Blood Glucose Index (LBGI), $GRADE_{\%hypoglycemia}$, Hypoglycemia Index), and measures of hyperglycemia (% in hyperglycemic range, High Blood Glucose Index (HBGI), $GRADE_{\%hyperglycemia}$, Hypoglycemia Index).[11,12]

The %CV and SD are the most popular metrics for GV for patients, clinicians, and researchers because of their simplicity, relative familiarity, and unambiguity.[11–12,33–38] %CV is correlated with risk of hypoglycemia.[32–38] The relationship is not a direct proportionality: If %CV is less than 25%, then risk of hypoglycemia is extremely low, almost negligible. However, when %CV reaches and exceeds 25%, there is a nearly linear relationship both theoretically[38] and empirically.[38] %CV is very weakly correlated with mean glucose.[34,35] Mean glucose is weakly inversely related to risk of hypoglycemia.[35] SD is moderately correlated with mean glucose, but very weakly related to risk of hypoglycemia.[33–38]

"Classical" measures of variability

F. J. Service clearly distinguished within-day and between-day variability.[3,39] However, the two ''classical'' measures of variability that he described (MAGE and MODD) are infrequently used today. Both are highly correlated with SD_T, with each other, and with several other metrics of variability (SD_w, SD_b, $CONGA_{24}$).[11,12,30–34]

Mean Amplitude of Glycemic Excursion. Manual or graphical estimation of MAGE is subject to many sources of error. Unfortunately, the use of computer programs only partially resolves this problem: different programs can give markedly different results.[40] These discrepancies appear to be due to several factors: different definitions, algorithms, and the extent of preliminary smoothing of the glucose-versus-time curves. Some of the ambiguities include the following:

- Should one calculate the amplitude of the excursion using upstrokes ($MAGE_+$), downstrokes ($MAGE_-$), perhaps depending on which occurs first as in the original definition,[3] or both upstrokes and downstrokes[41]? Should one first calculate the amplitudes separately for upstrokes and downstrokes and then calculate an average or weighted average ($MAGE_{avge}$)[41]?
- Sometimes it is difficult or impossible to determine whether there is a true apex or nadir, or whether there is a ''shoulder'' or random noise on a curve that is otherwise continuing its upward or downward trend.[41]
- A peak is defined only when the excursion amplitude exceeds an arbitrary level of 1 SD.[3] Unfortunately, the SD may change significantly during a multiday or multiweek glucose time series, so it is not clear what value of SD one should use when calculating MAGE.
- The relationship between MAGE and postprandial peaks has never been clarified. Service noted that it was never his intention to regard MAGE to be a measure of postprandial peaks.[3]

Mean Of Daily Differences. Measures of between-day variability, for example, MODD,[39] $MODD_1$,[11,12] SD_b, and $CONGA_{24}$, implicitly assume that the individual is continuously experiencing a stable and almost perfectly reproducible pattern of meals, physical activity, and medications on successive days–as might sometimes be possible within a very constrained clinical research facility[3,39] but not in a real-world, free-living ambulatory setting. It might be preferable to synchronize glucose values obtained using an eight-point glucose profile (before and after meals, bedtime, and overnight [3–4 AM]),[42] as was standard practice when glucose data were obtained using SMBG and recorded in cells in a logbook corresponding to *categories* of time of day.[42,43]

Postprandial excursions. Service proposed three criteria to characterize postprandial excursions in his 1987 article,[3,39] G_{max} maximum postprandial glucose for any one meal; T_{max}, the time after onset of the meal when G_{max} occurs; and %Recovery from the peak glucose toward baseline, evaluated 1 h following T_{max}. Unfortunately, any large systematic change in glucose with time in the hours before the meal, indicating an unstable baseline, can make it difficult to measure these parameters accurately. Additional criteria may be needed.

Postprandial excursions: Additional methods

One approach, applicable to both SMBG and continuous glucose monitoring (CGM), is to calculate, for each of the three major meals, the mean change in glucose from immediately premeal to a fixed time following the meal (e.g., 2 h), together with its SD and SEM. Ideally, this should be done using pairs of glucose values obtained on the same day to eliminate the effects of between-day variability. When using CGM, one can use the area under the curve above the premeal baseline for a prespecified time following the meal (e.g., 4 h).

One can plot glucose by time of day.[43,44] Since the postprandial excursion can vary substantially from day to day, we need a way to combine and extract data from multiple days. A large portion of day-to-day variability for any specified time of day depends on changes in the subject's schedule for meals, medications, and activity. For example, dinner might occur any time during a range of several hours. This can shift the entire profile (as related to dietary intake and any associated medications) and would be expected to result in a large variability in glucose profiles by time of day. If we simply average the profiles, using clock time, this will result in large values for metrics for between-day variability. Blurring or jitter of events on profiles is readily observed in the AGP[44–49] and can result in significant loss of resolution. One can try to restore the temporal resolution by virtue of the ''law of large numbers'', that is, simply by averaging from multiple days. It is often necessary to average glucose data from 2 or 3 weeks[44,46,47,50,51] to obtain an average (or median) that is similar to the underlying patterns on individual days. There is degradation of the pattern due to averaging: the amplitude of the ''mean glucose peak following dinner'' will be smaller, the amount of scatter around that average will be larger, and the duration of the ''peak'' will be longer than the typical pattern observed for any one day.[49]

One approach to this problem is to select segments of the glucose profile (e.g., 2 h before to 4 h following a major meal) and synchronize these patterns according to the time of initiation of the meal. This should effectively neutralize the blurring due to variability in the time of onset of meals. This synchronization should be combined with a baseline correction so that the premeal glucose is taken as zero.[49] After combining data from multiple meals of the same type obtained on different days, one can display the percentiles (e.g., 10^{th}, 25^{th}, 50^{th}, 75^{th}, and 90^{th}) for glucose increment above baseline for any time after the start of the meal. This can improve our ability to characterize the median postmeal glycemic excursions for major meals and the ability to characterize day-to-day variability in meal profiles in terms of amplitude, duration, shape, and area under the curve.[49]

Variability of glucose profile patterns from day to day

Between-day variability can be quantified by:

(a) SD of daily mean (SD_{dm}), and between-day variability (SD_b);
(b) Changes in a simplified categorized glucose distribution (%hypo-, %target- and %hyperglycemia) from day to day.[52] Unfortunately, these two approaches do not address between-day changes in *glucose patterns by time of day*.
(c) A popular method is to simply superimpose glucose profiles from several successive days. This approach is neither quantitative nor objective, and becomes impractical when dealing with more than 7 days of data.
(d) A quantitative approach to this analysis would be to take the CGM data for a specified block of time (e.g., 15 days), calculate the average pattern by time of day (mean or median glucose for each hour), plot these values on the horizontal axis, and plot the glucose values for the same time of day for each separate day on the vertical axis. If an identical glucose pattern were present for all days in the series, then all of the data points would fall on the line of identity.[11,12] A regression line through these glucose data points should have a slope of 1.0 and an intercept of zero. We can calculate the SD or root mean square (RMS) error of the glucose data points around the line of identity (RMS) for each day and evaluate whether some days appear to be outliers.[11,12] One can compare this metric for day-to-day *variability in glucose patterns* for any one person to that observed in a reference group.

This kind of analysis can be more informative than examining numerical values for several metrics (e.g., SD_{dm}, SD_b, $SD_{b//dm}$, $CONGA_{24}$, $MODD_1$) which reflect the magnitude of between-day variability but do not address the question of stability of glucose patterns from day to day.

Systematic changes of glucose profile patterns related to day of the week

After evaluating the day-to-day variability in glucose values and the stability or instability in glucose patterns by time of day, one needs to address a separate question: Is variability between days occurring in a purely random manner, or is it related to day of the week per se? Such variations might be related to different schedules for meals,

work, school, medications, physical activity, and sleep on different days of the week.

There are several ways this question could be addressed. We might want to evaluate questions, such as the following:

Does the shape of the glucose profile on Mondays more closely resemble those observed on other Mondays than the profile (pattern) from other days of the week?

Are there systematic differences in the glucose profile patterns obtained on Wednesdays and Saturdays?

Are patterns observed on weekends similar to those observed on workdays or schooldays? Are patterns different on holidays?

It may be necessary to custom tailor the procedures for evaluating these kinds of hypotheses. However, when looking for obvious changes in glucose profile patterns by day of the week, one would like to have a simple general approach such as the following:

- One can calculate the average glucose pattern calculated for all days of the week combined, possibly collected over a period of one or 2 months, so we have at least four and preferably eight glucose profiles for each day of the week. We can then examine correlations for glucose by time of day for each day of the week with the overall average pattern for all days. The correlation coefficients serve as crude indicators of similarity. This analysis might show two or more subsets of days of the week that have similar patterns by time of day and are highly correlated with the average profile, while another subset of days of the week might have a very different degree of correlation with the overall pattern.
- One can calculate the correlation coefficients for all 21 possible pairwise comparisons of 7 days. In this manner, one might find that glucose patterns on some days of the week are similar, while other days have different patterns. One can then characterize the typical pattern for different subsets of days of the week. If the patient and caregivers are aware of systematically different patterns on different days of the week, it may be easier to identify some of the underlying factors responsible. These kinds of analyses can also be applied to SMBG glucose data if the patient is consistently obtaining the traditional eight-point glucose profile related to meals, bedtime, and overnight.

If different patterns are observed on different days of the week, one might want to request that the analysis software display the AGP (described further in the following section) for specific days or combinations of days of the week. This should be more informative than the heterogeneous smear obtained when one superimposes datasets with consistently different patterns, especially with respect to predicting risks of hypo- or hyperglycemia by time of day and day of the week.

A graphical method has been developed to facilitate examination of the effects and interactions of date, time of day, and day of the week in terms of their effects on glucose patterns, using a simplified color-coded two-dimensional view showing multiple glucose categories.[53]

Graphical Displays

Some of the best ways to evaluate GV involve use of graphical displays. These enable one to identify patterns, changes in patterns, outliers, and to identify the dates, times of day, and days of the week associated with the largest departures of glucose from the target range and the greatest risk of hypo- and hyperglycemia. The graphical displays usually do not require familiarity with statistical methods, are often regarded as ''intuitive,'' not requiring any model or assumptions, and readily understandable by both physician and patient. Table 2 is a partial listing of some of the available forms of graphical display.

Graphical displays convey information regarding glucose variability in a direct, intuitive, qualitative manner. Several graphical displays have been used extensively both for blood and interstitial fluid glucose: glucose frequency distributions, simplified glucose distributions using ranges or categories for glucose,[52] glucose versus *date*[43] glucose versus *time of day*[40–49] (*AGP*), and glucose versus day of the week.[45,50–53]

(1) Simplified Glucose Distribution. Most clinicians and patients are not familiar with use of frequency distributions (histograms) or cumulative frequency distributions, and these graphs fail to indicate the percentage of glucose values falling in a series of specified ranges (target range, hypoglycemic ranges, hyperglycemic ranges). A *simplified* frequency distribution, showing the percentage of values (or of time) within each of those three ranges was introduced by Rodbard,[52] has been endorsed by five committees,[6–9,48,54] and has been incorporated into several commercially available software programs. These stacked bar or column charts can be constructed for each day or all days, for the entire day or for selected time segments within the day, in relationship to meals and sleep (when analyzing eight-point glucose profiles for SMBG),[43] by day of the week, and by date.[52]

Table 2. Graphical Displays of Glucose for Clinical Use

Graphical displays
• Glucose frequency distribution: (simplified) using 3 to 7 categories for glucose
• Glucose by date: glucose values (mean, and for selected times of day); Box Plots; % within several specified ranges (simplified glucose distribution)
• Glucose by time of day: Ambulatory Glucose Profile (AGP)
• Postprandial glucose profiles above premeal baseline glucose for major types of meals: synchronized, showing percentiles for glucose by time after onset of the meal
• Glucose by day of week: Box plots, % within several specified ranges,[52] AGP for each day of the week using data pooled over multiple weeks

(2) Glucose versus date: A graph of glucose values versus date allows one to identify changes due to therapeutic interventions, intercurrent illness, and major lifestyle events. When displaying glucose as a function of date, one may use the original glucose values (overall mean or glucose values for specified times of the day). Or, one can use a simplified frequency distribution, showing the percentage of glucose values in categories ranging from very low to target range to very high, also as a function of time.[52]

(3) Glucose by time of day: One may elect to use a simplified categorized time axis, corresponding to an eight-point glucose profile: fasting, after breakfast, before lunch, after lunch, before dinner, after dinner, bedtime, and overnight (3–4 AM). This was the standard method for display when using SMBG. It has the advantage of being relatively insensitive to changes in the timing of various meals. Rather than simply showing the glucose values, one can use a Box plot (0^{th}, 25^{th}, 50^{th}, 75^{th}, and 100^{th} percentiles)[43] indicating the median, IQR, range, outliers, and mean ± SEM.[43]

One can also display the simplified glucose distribution in the form of a stacked bar chart, by time of day, pooling data from multiple days.[52]

(4) Postprandial excursions: One of the major sources of variability in glucose levels is the postprandial excursion. One can characterize this using simple statistics, for example, the postprandial maximum glucose (G_{max}) and the time following the meal when it occurs (T_{max}),[39] the increment between premeal baseline and the postmeal maximum glucose, or the area under the curve above the baseline (premeal) glucose. One can plot glucose following each major type of meal, synchronized with respect to the start of the meal. However, one can also plot the *increment* in glucose above the premeal glucose. One can then calculate an average (mean or median) using data from several days and apply smoothing. One can estimate the various percentiles for glucose at any specified time following the onset of the meal. In effect, one can create an ''AGP'' for glucose values following meals, synchronized with respect to the onset of the meal, and ''baseline subtracted'' so that we are monitoring the glucose excursion. One can then evaluate the Area Under the Curve (AUC) using the median curve, and test whether profiles for breakfast, lunch, and dinner are similar in shape and/or magnitude.

(5) Glucose by day of week: The simplest approach is to display the mean glucose for each day of the week, together with a measure of its variability, for example, SD and SEM. The next step is to show a Box plot with the usual percentiles.[43] A third approach is to display the average glucose profile by time of day, for each of the day of the week, pooling data from 4 or more weeks, and superimposing the mean or median by time of day on a scattergram of the original glucose measurements.[45] A fourth method is the simplified glucose distribution (% of glucose values falling into several (e.g., 7) categories for glucose) by day of the week.[52]

Needs of the clinician

In view of the large array of metrics for variability, which metrics are most helpful for care of a typical patient? The plausible answers are: (1) mean or median glucose; (2) %CV; (3) a graph or table of a simplified glucose frequency distribution in the form of a stacked bar or column chart (% of glucose values in target range, % in hyperglycemic ranges, % in hypoglycemic ranges with options to display additional segments of the glucose scale,[6–9,48,52,54] graphs of glucose by date,[43] (5) graphs by time of day (AGP),[43–49] (6) graphs by day of the week,[52] and (7) graphs of glucose increments above premeal baseline synchronized with respect to time after the onset of meals.[49] These displays should be accompanied by information regarding frequency of hypoglycemic episodes, classified according to the American Diabetes Association (ADA) and the International Hypoglycemia Study Group (IHSG)[55] methodology.[6–9]

Ambulatory Glucose Profile

The AGP, the glucose profile by time of day, is one of the best ways to characterize the average glucose level and GV. We will review its basic features[43–49] and suggest several possible enhancements (Table 3).

(1) Scattergram: The AGP displays glucose data obtained during a period of time (usually 2 to 4 weeks),[44,46,47,50,51] by time of day. This results in a scattergram. One should display the thresholds for Level 1 and Level 2 hypoglycemia,[6,7,48] and identify the times of day when hypoglycemia occurs. Likewise, one should display the thresholds for Level 1 and Level 2 hyperglycemia[6,7,48] and note the times of day when those events occur. Sometimes the scatter is so large that it is difficult or impossible to discern an underlying pattern. However, one can still locate the maximum and minimum, and hence the range. The AGP can be enhanced by display of the glucose frequency distribution (histogram) or a Box plot showing all glucose values aligned on the same vertical axis adjacent to the right-hand axis for the AGP.[43] For analysis of the vitally important overnight period, a noon to noon or a 48-h display can be helpful, as has been used in studies of activity monitoring.

(2) Fiftieth percentile by time of day: By display of the median (50th percentile) for each 30- or 60-min time period throughout the day, typically from midnight to midnight, and connecting those medians with a smooth curve, the overall trend of glucose by time of day immediately becomes apparent.[43–49] This indicates the extent of the variability of the average pattern by time of day, a parameter designated as $SD_{hh:mm}$, that is, the SD of the smoothed mean or median glucose by time of day. This is an underestimate of the true within-day variability because of the effects of smoothing, heterogeneity, and asynchrony of patterns on different days.

IQR, 25th and 75th percentiles, by time of day: By superimposing a display of the smoothed 25th and 75th percentiles for each hour of the day (again, connected with continuous smooth curves) one can see the range for the central 50% of glucose values.[43–49] This IQR for each

Table 3. Ambulatory Glucose Profile: Glucose by Time of Day, with Proposed Enhancements

Ambulatory glucose profile

1. Scattergram of glucose values by time of day
2. Smoothed profiles of percentiles (2.5^{th}, 5^{th}, 10^{th}, 25^{th}, 50^{th}, 75^{th}, 90^{th}, 95^{th}, and 97.5^{th} percentiles) by time of day, indicating median (50^{th} percentile) and IQR (75^{th}–25^{th} percentile)
3. Options for display of the smoothed percentiles superimposed on the scattergram for glucose observations, and ability to interactively cycle through multiple types of displays to show the desired percentiles with or without the glucose data points
4. Options for use of log scale for display of glucose values, thereby expanding the hypoglycemia range and compressing the hyperglycemia range.[56]
5. Display of risk of hypoglycemia by time of day (observed, estimated,[38] or predicted)
6. Display of risk of hyperglycemia by time of day (observed, estimated,[38] or predicted)
7. Display of frequency distribution for all glucose values obtained at all times of day in one or more of three popular forms: histogram, box plot,[43] or stacked column chart[52]
8. Analysis of meal-related patterns of glycemia, for major meals:
   a. Distribution of timing of meal
   b. Distribution of premeal baseline glucose and of premeal slope of glucose versus time
   c. Distributions of maximal postmeal glucose (G_{max}) and the time when it occurs (T_{max})[39]
   d. Postprandial glucose excursion by time after initiation of the meal (Area Under the Curve (AUC) above premeal baseline)
9. Display of glycemic variability within narrow (e.g., 3 h) time segments by time of day (e.g., $SD_{ws\ h}$ with $h = 3$ vs. time of day)
10. Interactive analysis and interpretation of the AGP: For example, ability to select any one glucose value and obtain information regarding date, time, numerical glucose value, and statistics (mean, SD, etc.) for any given day or local segments in terms of date, time of day, relationship to meals, and day of the week
11. Display of AGP for selected subsets of days of the week with similar patterns
12. Display of doses of medications (including insulin administration and insulin-on-board) and of physical activity (timing, intensity, duration)
    by time of day, using the same timeline as glucose
13. Ability to display the horizontal time axis with adjustable starting points (e.g., midnight to midnight, noon to noon, option for a 48-h display)
14. Evaluation of data density: glucose measurements per hour

hour of the day provides a robust and reliable estimate of glucose variability, making it possible to examine the extent to which GV changes systematically by time of day. The IQR as displayed on the AGP primarily reflects between-day variability (SD_b).[11,12] Between-day variability is highly correlated with and approximately the same magnitude as total variability (SD_T) and within-day variability (SD_w). The difference between the 25^{th} and 75^{th} percentiles would correspond to ~ 1.35 SD if the underlying distribution was Gaussian. This approximation is fairly good, even with the degree of asymmetry encountered with glucose distributions in people with diabetes.

Tenth and 90^{th} percentiles by time of day: By superimposing two more smoothed curves, for the 10^{th} and 90^{th} percentiles, respectively, one can immediately see where 80% of the glucose values fall by time of day.[46,47] These two curves also allow one to see when glucose values are falling close to the limits for hypoglycemia, Level 1, 70 mg/dL (3.9 mmol/L) or Level 2, 54 mg/dL (3.0 mmol/L).[6,7,50] Likewise, it enables one to identify the times of day when the glucose is falling close to a hyperglycemic range Level 1, 180 mg/dL (10 mmol/L), or Level 2, 250 mg/dL (13.9 mmol/L). The distance between the 10^{th} and 90^{th} percentiles would correspond to 2.56 SD for a Gaussian distribution.

If one has very high-density data (e.g., when superimposing 30 to 60 days of CGM data), one might also like to visualize the 5^{th} and 95^{th} percentiles (a 90% confidence interval), and possibly even the 2.5^{th} and 97.5^{th}, percentiles (a 95% confidence interval).

(3) Superposition of Percentiles and Glucose scattergram: It is highly desirable to be able to display the glucose scattergram superimposed on the percentiles (or selected percentiles). This display indicates the data density (based on the glucose datapoints), and helps one evaluate how well the percentiles have been fit to the datapoints, and whether the degree of smoothing is appropriate.

(4) Logarithmic scale for glucose: To date, nearly all uses of the AGP and other graphics have displayed glucose on a linear scale.[43–49] Rodbard proposed use of log(Glucose) to compress the hyperglycemic region and expand the hypoglycemic region, making it easier to identify hypoglycemic events and thereby obtain a more ''balanced view of hypo- and hyperglycemia''.[56] This improves the symmetry of the distribution. For people unfamiliar with log scales, several alternative nonlinear compression/expansion scales could be used.

(5) Risk of hypoglycemia: When the 10^{th} percentile for glucose approaches 70 mg/dL (3.9 mmol/L), one can

immediately infer that this is a time of day when risk of hypoglycemia is significant. However, it is better to display a measure of the risk of hypoglycemia by time of day. This can be shown as the *observed* probability that a glucose value will fall below any specified threshold (e.g., 70 mg/dL, 3.9 mmol/L) during any specified hour of the day. Alternatively, one can display curves for two thresholds, for example, 70 and 54 mg/dL. These probabilities can be shown as smooth curves displayed below the time axis for the AGP itself. In lieu of the *observed* percentage of glucose values observed to fall below any given threshold, one could display LBGI[5] (a well-validated predictor of hypoglycemia), or an estimate of the risk of hypoglycemia calculated on the basis of the mean, SD, and shape of the observed glucose distribution for each hour of the day.[38]

(6) Risk of Hyperglycemia: As in the case of hypoglycemia: If one observes that 25% of the glucose values are above 180 mg/dL (10 mmol/L) or 10% are above 250 mg/dL (13.9 mmol/L), one can immediately conclude that there is a major problem with hyperglycemia. It would be more informative to display a direct measure of risk of hyperglycemia such as the *observed* percentage of glucose values above a specified threshold as a smoothed curve versus time of day. Alternatively, one could plot the smoothed HBGI[5] by time of day, or the estimated risk of hyperglycemia based on the mean (or median), SD, and the empirically observed shape of the glucose distribution (Gaussian, log-Gaussian) at that time of day, pooling data from multiple days.[38]

(7) Display of frequency distribution for glucose values obtained at all times of day, using a histogram or ''clinical histogram''[43] showing all glucose values, including percentiles (especially the 25th, 50th (Median), and 75th percentiles), and Mean ± 1 SEM.

(8) Analysis of glucose levels and patterns in relationship to each type of major meal:

   (A) Distribution of timing of onset of meals
   (B) Distribution of premeal baseline glucose and prior slope of glucose versus time
   (C) Distributions of maximal postmeal glucose (G_{max}) and of timing of the maximum (T_{max})[39]
   (D) Postprandial glucose excursion pattern by time after initiation of the meal
   (E) Area under the curve for glucose following onset of a meal (mean, SD, and SEM)

(9) Display of GV by time of day: One can plot a measure of GV, for example, the SD of glucose values during a 3-h period, $SD_{ws\ 3}$, by time of day. This provides a quick overview of how GV changes depending on time of day. Alternatively, one could use SD_b, $MODD_1$, or $CONGA_{24}$ calculated for a moving 3-h window, combining results from several days.

(10) Interactive analysis of AGP: When the AGP is viewed online, or in other interactive systems, it would be desirable to have the ability to select a single glucose data point and immediately obtain the date, time, glucose value, and ancillary information. Furthermore, one would like to be able to obtain additional analyses, regarding glucose statistics for the same day, for a time period within a day, or for a similar time period within a range of days. An interactive system would also allow one to customize the display (e.g., provision of options to use a log scale for glucose, and to display the glucose scattergram, percentiles, or both), or select various animated displays presenting the major findings in a slide-show mode.

(11) AGPs for selected days of the week exhibiting similar patterns:
Since the glycemic profile may vary consistently depending on day of the week, it would be desirable to enable the software to display the AGP separately for selected days of the week.

(12) Display of medications, physical activity, and diet (including basal and bolus insulin) by time of day: One can display the dose and timing of all medications, and also show model-predicted plasma insulin levels and model-predicted pharmacodynamics (glucose production and disposition) using models with representative population-level parameters. The graphical display should incorporate data from as many major relevant factors as possible (medications, carbohydrate intake, physical activity).

(13) Options to display time of day with arbitrary starting point (e.g., midnight to midnight, noon to noon, 6 AM to 6 AM, etc.), or to use a 48-h display for better display of the nocturnal period.

(14) Display of data density: For SMBG, it is instructive to plot the frequency of glucose measurements by time of day for the 24-h period, to identify times of day when it would be desirable to obtain more glucose measurements. If the number of glucose values per hour falls below a specified threshold, then the curves for median and other percentiles can be suppressed, as in the original proposal for the AGP.[44] This is less of a problem for CGM, where, presumably, glucose values are obtained at a rate of 12 per hour, around the clock, so data density should be uniform unless there were problems with the sensor.

Time Series Analysis of Glucose Monitoring Data

Fourier analysis and power spectral density

Miller et al.[14] and Strange et al.[15] may have been the first to apply Fourier analysis to glucose time series based on CGM. They characterized glucose patterns by time of day for each subject for a 24-h period. More recently, Strange et al.[15] applied this methodology to evaluate glycemic periodicity in children and adults with type 1 diabetes and in adults with T2D. They observed a significant loss of high frequency oscillations in type 1 DM in *adults* compared with *children*, and a loss of energy associated with high-frequency oscillations in people with type 2 diabetes, especially those receiving progressively more intensive forms of therapy. The authors regard intensity of therapy as a surrogate marker of duration of diabetes and extent of progression of beta cell loss. (15, and Poul Strange, personal communication).

Fico et al. utilized spectral power density analysis, using the fast Fourier transforms and the Welsh method, to show a progressive loss of high-frequency oscillations in glucose as one moves from ''people at risk for development of diabetes'' (presumably prediabetes), to subjects with

recent onset or longstanding T2D or T1D.[21] Their findings also suggest the loss of power (energy) in rapid oscillations as T2D progresses and the increasing dominance of low-frequency oscillations. However, the two analytical methods used by these authors provided inconsistent results.[21]

Metrics for variability which depend on frequency of oscillation relative to frequency of glucose measurement: Mean Absolute Glucose change per unit time, Distance Traveled, and GVP

Mean absolute glucose change per unit time. Hermansen and DeVries noted that metrics such as SD were completely insensitive to the frequency or periodicity of glucose changes, and proposed a new metric, (Mean Absolute Glucose (MAG) *change per unit time*).[2,4] *The words ''change per unit time'' were not included in the acronym for MAG, but were included in the formula for calculation.* MAG is calculated as the total absolute changes in glucose levels between successive pairs of points, divided by the total time interval. Kohnert et al. showed that MAG correlated poorly with other measures of GV, such as SD and MAGE, was dependent on frequency of glucose measurements and on whether the time intervals between glucose measurements were constant or variable.[57] The value of MAG depends on the choice of units used for glucose (mg/dL, mmol/L) and for total elapsed time, but not on the units used for the time interval (Δtime) between successive glucose measurements.

Distance traveled. Marling et al. proposed a very similar metric, ''Distance Traveled (DT)''.[17] Initially, she did not indicate that the DT should be normalized by the total duration of the period observation, although her later studies utilized a fixed duration of 24 h.[18] DT refers to the *vertical* direction on a graph of glucose versus time, which is obtained as the summation of the absolute changes in glucose levels between successive values, exactly as for MAG.

Glycemic Variability Percentage. Peyser et al.[19] proposed a metric that is closely related to MAG and DT, designated as glycemic variability percentage (GVP). This metric calculates the total length (L) of the line segments connecting successive glucose values on a graph, over and above the minimal length of a flat line segment of similar duration (L_o), expressed as a ratio to L_o:

$$GVP = 100\ ((L - L_o)/L_o) = 100\ (L/L_o - 1)$$

Caveat: Numerical values for GVP depend on the choice of units used for time interval between successive glucose measurements, Δt, as this affects the relative contributions to the length of the hypotenuse connecting successive glucose data points attributable to changes in glucose (ΔG) and those due to changes in time (Δt). Values for GVP can change dramatically depending on whether one uses mg/dL or mmol/L for glucose and seconds, minutes, hours, or days as the units for Δt. GVP is unaffected by the choice of total elapsed time, since L is expressed relative to L_o.

Hirsch et al.[58] reported differences in GVP for adults, adolescents, and children with T1D. This is qualitatively consistent with the reports by Strange and Miller.[15] Garcia et al.[20] showed differences in GVP for people with T1D using a bihormonal (''bionic'') closed-loop system compared with subjects using open loop control: the closed loop resulted in a decrease in SD and MAGE but an increase in GVP. Presumably, this discrepancy is due to the presence of small, high-frequency fluctuations or oscillations that contribute to GVP, but not to the overall SD or MAGE and other measures of ''macro'' variability.

Kovatchev and Cobelli[5,59] emphasize the desirability of characterizing CGM data as time series as opposed to static frequency distributions. Cobelli implied that development of methods such as GVP to characterize GV was unnecessary[59] and restated his preference for the methods such as a frequency distribution for Rate of Change of glucose ($\Delta G/\Delta t$), the Poincaré plot, and Variability Grid Analysis.[5,59] Ironically, GVP[19,20,58] was able to detect the several kinds of rapid oscillations as identified by traditional methods of time series analysis,[14,15,21] and was used successfully to make novel observations of clinical and pathophysiological significance.[19,20,58]

Multiscale entropy and complexity analysis. Chen et al. and Costa et al.[22–24] used different measures of ''complexity'' and multiscale entropy (MSE) to demonstrate loss of complexity of glucose time series in people with progressively longer duration of diabetes.[23,24]

Zhang et al.[25] used similar mathematical approaches to show that two experimental animal models of type 2 diabetes, the ob/ob mouse and Zucker fatty rats, displayed progressive loss of complexity of glucose time series. Zhang used a novel methodology to obtain intra-arterial glucose levels at ten-second intervals for a sustained period, with calibrations every 12 h.[25]

Kohnert et al. provides a review of some of these findings[26] and analyzed an additional dataset for people with T2D: as the quality of glycemic control decreased progressively, as measured by increases in the Q-Score,[60] GRADE score,[61] or Average Daily Risk Range (ADRR),[5,62] or was associated with use of progressively more intensive forms of antidiabetic therapy, there was a systematic decrease in the MSE index.

The studies using Multistate Entropy[22–26] appear to be consistent with the results of Strange et al.,[15] Fico et al.,[21] Hirsch,[58] Peyser et al.,[19] and Garcia et al.[20] There is a need for additional studies to confirm and expand these findings.

Discussion

The results reported using time series analysis, GVP, and MSE raise several methodological questions. Are these analytical methods measuring the same phenomena? It would be important to analyze the datasets from these[14–26,58] and similar studies to evaluate whether these diverse analytical methods are detecting exactly the same phenomena. It might then become possible to further optimize the metrics employed. The results of analysis by GVP (or DT and MAG) are highly dependent on the frequency of glucose measurements: the higher frequency events should become undetectable if longer time increments (Δt) are used, or if data are subjected to preliminary smoothing. The MSE methods exploit this property by systematically changing the ''coarseness of the grain'' for sampling frequency. Does loss of high-frequency oscillations result in a decrease in MSE and decreased complexity both qualitatively and quantitatively? Do the two methods for power spectral density and periodograms used by Fico et al.[21] indicate oscillations of the same frequencies as the method of Miller and Strange[14,15] when applied to the same dataset?

Zhang et al. speculated that the progressive loss of complexity in glucose time series might permit earlier detection of type 1 or type 2 diabetes both in man and experimental animals.[25] It remains to be seen which methodology and criteria might be most sensitive and specific for detection of progression of type 1 diabetes, prediabetes, and type 2 diabetes. Would any of these methods be able to detect incipient onset of type 1 diabetes?

If we are trying to distinguish dominant rapid oscillations with a period of $\sim$3–4 h[15] as observed for normal subjects, and dominant periodicities of 12–24 h or longer in both type 1 and type 2 diabetes,[15,21] then there might be other approaches that would be easier to understand by people with less familiarity with time series analysis. Perhaps use of a ratio of $CONGA_{n1}$ to $CONGA_{n2}$ or similar approaches would be able to identify loss of the rapid oscillations. Possible values for n_1 and n_2 might be 3.5 and 18 h, respectively.

Are the rapid glycemic oscillations observed by Garcia et al.[20] a property of *dual*-hormone (insulin+glucagon) closed-loop systems, or would they also be observed with single-hormone (insulin) closed-loop systems? Do they depend on the nature and tuning of the control algorithm? Are these oscillations consistent with the frequency spectrum in people without diabetes, or are they a property of the dual-hormone control system? What would happen if one were measuring *blood* glucose every 10 s as in the methods used by Zhang,[25] or if one were using more rapidly acting insulins (Faster Acting Insulin Aspart)[63] or intraperitoneal insulin infusion[64]?

There is a need for a better understanding of the practical pros and cons of traditional time series approaches,[14,15,21] the GVP—MAG—DT approaches,[16–19] and the Complexity theory/MSE approaches.[22–26] Some of these should be addressed with both real CGM data and simulated data to examine sensitivity to features known to be present in the data. Further research into the mathematical, statistical, and engineering methodologies for characterization of GV is needed.

The author suggests that the recommendations for enhancement of the AGP provided above be tested in usability and cognitive laboratories with representatives from the intended user communities (patients, families, physicians, diabetes educators, and other healthcare professionals).

There is a need for databases of metrics from several populations of people with diabetes, so that results for the numerous metrics can be converted from their numerical values to percentiles,[34] or nearly equivalently, to z-scores for an appropriate reference population.[60] It remains to be seen, just how some of these analytical methods can be incorporated into artificial intelligence systems to automatically provide clinical interpretations for a wide range of end-users, how rapidly that can be done, and how effective, safe, and robust such systems will be.

It is important to distinguish between criteria for glycemic variability[1–5,11,12,16–20] and criteria for overall quality of glycemic control.[11,12,34,35,50,58,60–62,65]

Conclusions

There are multiple types of GV: minute-to-minute, hour-to-hour, day-to-night, day-to-day, weekday-to-weekend, month-to-month, and many others. Despite the desire to standardize on a small number of metrics, it is more important to be aware of the panoply of available methods and implement them in a manner consistent with fundamental statistical and data analytical principles. For routine clinical use, a few graphs, including but not limited to an *enhanced* AGP, and a few statistics (mean glucose, %CV, %hyperglycemia, % within target range, %hypoglycemia) are usually sufficient to characterize GV. Examination of glucose profiles by time of day, of synchronized postprandial increments above the premeal baseline glucose, and of stability of glucose patterns over a period of days and by day of the week, can be very helpful clinically. New methods are presented for analysis of postprandial excursions, day-to-day variability in glucose patterns, and systematic changes in glucose profile patterns by day of the week.

Several types of time series analysis (Fourier transforms, periodograms, power spectral density, Multiscale Entropy (MSE), and Glycemic Variability Percentage (GVP) have revealed progressive loss of ''power'' in high-frequency–low-amplitude glucose oscillations, and loss of complexity (decreasing MSE) during progression of both type 1 and type 2 diabetes, with more high-frequency glucose oscillations remaining in children and adolescents compared with adults with type 1 diabetes, differences between adults with type 1 and type 2 diabetes, and identifiable changes in people ''at risk for diabetes.'' Similar changes related to progression of diabetes were reported for two animal models of diabetes. Small rapid oscillations were observed in people with T1D using a dual-hormone closed-loop control. Further studies of GV are needed both to assist clinical management of patients and to achieve better understanding of the underlying pathophysiology of diabetes.

Author Disclosure Statement

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