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ORIGINAL ARTICLE

Multiplicative Surrogate Standard Deviation: A Group Metric for the Glycemic Variability of Individual Hospitalized Patients

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Abstract

Objective:

Group metrics are described to quantify blood glucose (BG) variability of hospitalized patients.

Methods:

The "multiplicative surrogate standard deviation" (MSSD) is the reverse-transformed group mean of the standard deviations (SDs) of the logarithmically transformed BG data set of each patient. The "geometric group mean" (GGM) is the reverse-transformed group mean of the means of the logarithmically transformed BG data set of each patient. Before reverse transformation is performed, the mean of means and mean of SDs each has its own SD, which becomes a multiplicative standard deviation (MSD) after reverse transformation. Statistical predictions and comparisons of parametric or nonparametric tests remain valid after reverse transformation. A subset of a previously published BG data set of 20 critically ill patients from the first 72 h of treatment under the SPRINT protocol was transformed logarithmically. After rank ordering according to the SD of the logarithmically transformed BG data of each patient, the cohort was divided into two equal groups, those having lower or higher variability.

Results:

For the entire cohort, the GGM was 106 (÷/× 1.07) mg/dl, and MSSD was 1.24 (÷/× 1.07). For the subgroups having lower and higher variability, respectively, the GGM did not differ, 104 (÷/× 1.07) versus 109 (÷/× 1.07) mg/dl, but the MSSD differed, 1.17 (÷/× 1.03) versus 1.31 (÷/× 1.05), $p = .00004$.

Conclusions:

By using the MSSD with its MSD, groups can be characterized and compared according to glycemic variability of individual patient members.

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Abbreviations: (BG) blood glucose, (GGM) geometric group mean, (MSD) multiplicative standard deviation, (MSSD) multiplicative surrogate standard deviation, (SD) standard deviation

Keywords: blood glucose, blood glucose metrics, blood glucose variability, critical illness, glycemic variability, hyperglycemia, hypoglycemia

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Introduction

Observational data suggest that, across a wide variety of settings and medical conditions, and perhaps independent of overall glycemia or hypoglycemia, the outcomes of hospitalized patients may be associated with glycemic variability. Our understanding of the impact of glycemic variability has been hampered in some studies by failure to apply variability metrics separately to the blood glucose (BG) distribution of each patient prior to analysis of group characteristics. Observational studies examining central tendency and dispersion of BG of each patient have been hampered by timing of BG tests at sporadic intervals. Additionally, we lack methodologies for controlling variability, by which a randomized, controlled trial might be attempted. In this article, we address an additional barrier, the lack of consensus on an appropriate metric for glycemic variability for hospitalized patients, by proposing use of a group metric that permits quantitative description and group comparisons of glycemic variability experienced by individual group members.

To study the impact of variability upon patient outcomes, it is important to recognize and quantitate patient-level glycemic variability of individuals and subgroups. In a number of studies, the standard deviation (SD) of the BG of the individual patient has been shown to correlate with hospital outcomes.[1–6] A major time-dependent change of overall glycemia could alter the dispersion of BG in relation to the overall mean BG on the time interval during which the sampling occurred, increasing the SD without necessarily signifying a pattern of recurring large oscillations.[7] It is acknowledged that infrequent sampling results in missing peaks and nadirs of BG. However, if the moving average of BG is relatively stable, and if timing of sampling is consistent, then SD may mirror the relative amplitude of typical glycemic excursions among patients within a group. Therefore, many authors consider the SD to be a variability metric. Despite its record of performance as a predictor of outcomes, the SD is misapplied when used for data sets that are not normally distributed. Population and individual patient BG distribution data typically are positively skewed,[8–10] such that use of SD for untransformed data is not appropriate for description of dispersion or for utilization of parametric statistical tests that assume a normal distribution of data. Studies reporting SD can yield results that could predict that some BG values would be less than zero among patients in the lowest BG range.[2]

Blood glucose data are often capable of being normalized by logarithmic transformation.[9–11] If original data generally have a distribution that is close to log normal, then the purpose of the logarithmic transform is to gain the advantages of representing the same data points as members of a normal distribution. The BG distribution characteristically seen has a positive skew (a long tail to the right), with mean greater than median. One advantage of performing logarithmic transformation is to put the data into a symmetrical form in which the mean approximates the median and the calculated SD creates specific expectations under an empirical rule, predicting the percentages of measurements falling symmetrically within 1 or 2 SDs of the mean. Group metrics can be performed on the logarithmically transformed data. If the transformation creates a normally distributed data set, then, assuming other conditions are met (such as independence of observations), between-group analyses using parametric tests are potentially valid. Reverse transformation serves the purpose of returning values that are in units of measure familiar to the reader on the same scale as the original data. A standard deviation that is added or subtracted in "log space" to give interval bounds becomes a multiplicative standard deviation (MSD) after reverse transformation. Interval bounds are given as a mean (±SD) in log space, or after reverse transformation, in more familiar units, the interval bounds are given as mean (÷/× MSD).

The purpose of this report is to describe a process for computing a specific descriptive group metric for glycemic variability experienced by individual patients, which we will call a "multiplicative surrogate standard deviation" (MSSD) of the BG. Use of such a metric has been suggested previously.[6] Here we wish to describe its multiplicative characteristics and the details of its application when used together with an artificial geometric mean, which would represent values characteristic of a group member of a cohort (an artificial patient). Since we believe the need for descriptive nomenclature has been a barrier to development of appropriate metrics, we suggest the names "geometric group mean" (GGM) and MSSD to succinctly denote the metrics described herein (**Figure 1**).

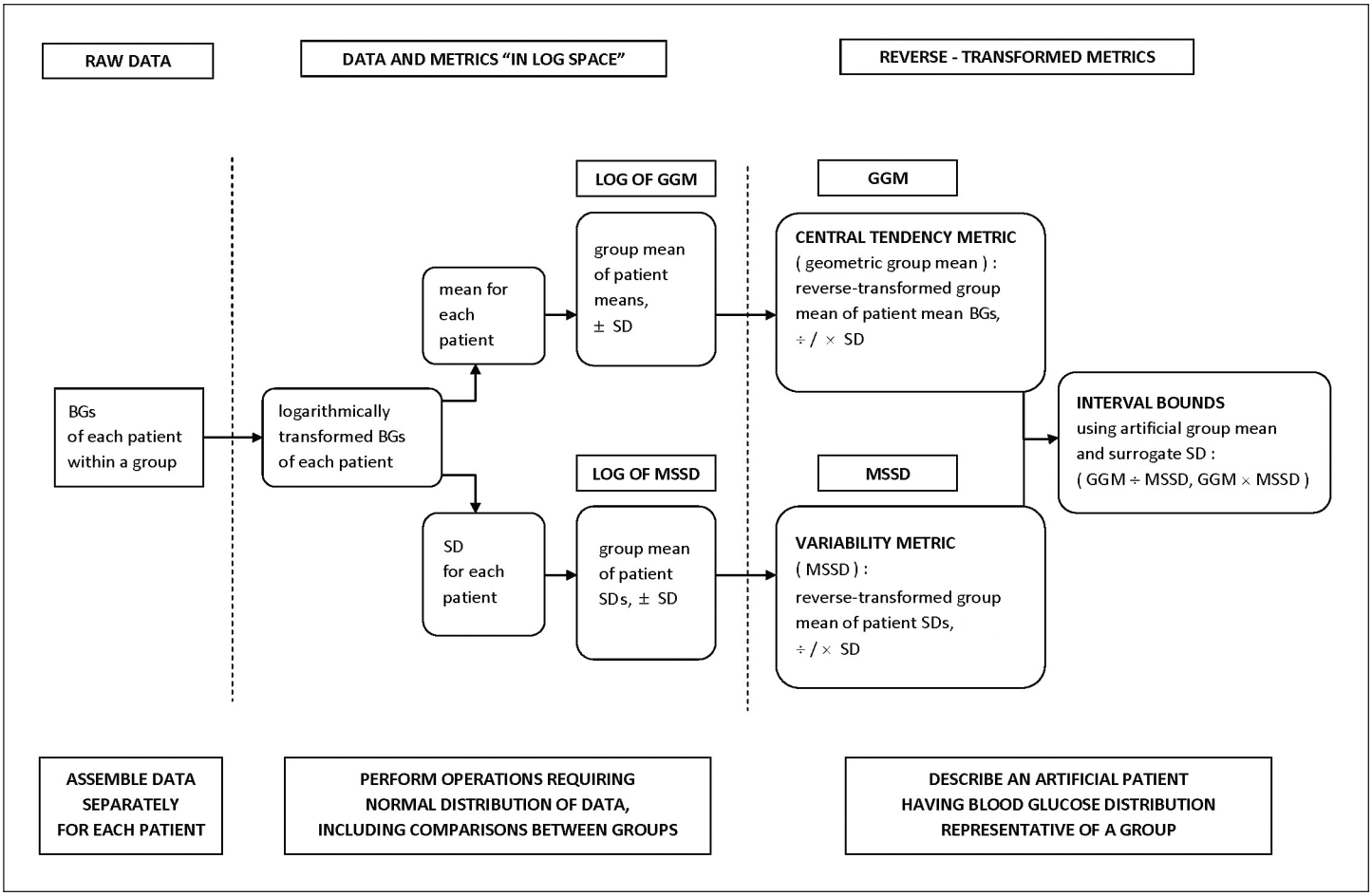

Figure 1. A process is depicted for calculation of GGM and MSSD intended to permit characterization and comparison of groups of hospitalized patients according to glycemic variability of patient members of each group. In case the collection of means or SDs of transformed BGs of each patient does not yield a normal distribution of these means or SDs, instead of using the SD, it would be appropriate to consider interquartile ranges and to use nonparametric testing for comparisons.

Methods

Description of Method

The purpose is to describe a variability metric representing dispersion of BG values of a typical single artificial patient as a characteristic of the group to which the patient belongs. In brief, the BG data of each group member is transformed logarithmically. The mean and the SD of the logarithmically transformed BG data are determined for each patient in the group. For the collection of the glucose means of the logarithmically transformed data of each patient, a group mean is computed, with its own SD, in log space. Using the logarithmically transformed glucose values, for the collection of SDs (one SD for each patient) a group mean is computed, with its own SD, again in log space. If groups of patients are to be compared using parametric or nonparametric tests, the comparisons should be performed in log space (**Figure 1**).

Reverse transformation is accomplished using the same base of the logarithm that was used during the initial logarithmic transformation of the BG values. The group mean of the patient means of logarithmically transformed BG is reverse transformed to give the GGM. After reverse transformation, the interval bounds of the first and second SD will be asymmetric about the GGM. Reverse transformation from log space of (mean – SD, mean + SD) and (mean – 2 SDs, mean + 2 SDs) gives interval bounds for GGM having the same predictive value as the first and second SDs determined in log space prior to reverse transformation, i.e., 68% of values for the population would fall within the first SD and 95% within the second SD. Alternatively, if the mean and its SD are reverse transformed from

log space separately, the reverse-transformed SD becomes a MSD for the GGM.[11] The same values for interval bounds associated with the first and second SDs are then given after reverse transformation by (GGM ÷ MSD, GGM × MSD) and (GGM ÷ MSD^2, GGM × MSD^2). The GGM is a group metric for central tendency of the patient BG.

The group mean of the patient SDs of logarithmically transformed BG is reverse transformed to give the MSSD. The interval bounds associated with the first and second SDs prior to reverse transformation from log space are then given by reverse transformation of each of the interval bounds (mean – SD, mean + SD) and (mean – 2 SDs, mean +2 SDs). Alternatively, if the mean and its SD are reverse transformed from log space separately, the same values for interval bounds associated with the first and second SDs then are given after reverse transformation by (MSSD ÷ MSD, MSSD × MSD) and (MSSD ÷ MSD^2, MSSD × MSD^2). The MSSD is a group metric for variability of the patient BG.

A true SD is defined only in reference to a single mean. The metric MSSD, derived after averaging the SDs of transformed BGs from multiple patients in log space, is not paired with any specific single mean and therefore is not properly a SD. Therefore, we suggest rather that the name should imply that that metric is a "surrogate" for a SD. This SD surrogate resembles an MSD. The surrogate SD is unitless. This SD surrogate has the magnitude characteristic of an MSD. When applied to a geometric mean BG that would be found in a BG distribution typical for a member of the sampled population, the MSSD yields values for interval ranges comparable in magnitude to an actual SD. If the MSSD is used in reference to GGM, it is used as follows: GGM, GGM ÷ MSSD, GGM × MSSD.

Method Applied to Demonstration Data Set

Previously published data will be used to demonstrate the method of analysis.[9] The data set is found at *http://www.journalofdst.org/Journal/pdf/July2008/VOL-2-4-ORG4-CHASE-DATA-SUPPLEMENT-DS1.XLS*.

For the present, a subset of BG data from time 0 to 72 h inclusive was examined for each patient in the cohort reported by Chase and coauthors,[9] a time interval chosen because each patient continued to have data beyond 72 h, but it was judged brief enough to capture differences in initial glycemic variability between patients. Some patients experienced brief gaps in data or compliance noted, but none were removed from treatment under the SPRINT algorithm for longer than 2 h during the interval of data collection.

The BG data set of each patient was logarithmically transformed. The SDs of the logarithmically transformed BG data sets were rank ordered, and the 20 patient members of the cohort were divided into two groups, having SDs of the transformed BG data set of each patient that were either below or above a value between the two median SD values, i.e., members were divided into "lower-variability" and "higher-variability" groups, each having 10 members.

The term "overall" when applied to mean or SD of a BG distribution will refer to the application of the metric to the set of all eligible BG data of the cohort (or a subgroup), using the BG as the unit of observation. For the entire cohort, and for the lower- and higher-variability patient subgroups separately, metrics were described in each of four ways (**Table 1**): (1) metrics from untransformed overall BG data, (2) metrics from untransformed BGs of each patient, (3) reverse-transformed metrics from logarithmically transformed overall BG data, and (4) reverse-transformed metrics from logarithmically transformed BG data of each patient. As final steps, reverse-transformed measures of central tendency, arithmetic SDs, and interval bounds were converted from International System of Units to conventional units, and results were rounded so as to have no decimal places. After use for other calculations, MSDs and MSSD in a final step were rounded to two decimal places for presentation as results.

For each of the four ways of describing metrics, the numbers of untransformed BG values were counted and proportions were determined that lay within the first or second interval bounds or outside of the second interval bounds for the entire cohort and separately for the lower- and higher-variability subgroups.

Using the unpaired two-tailed *t*-test with samples having unequal variance, first the overall means of the logarithmically transformed overall BG data between the lower-variability and the higher-variability patient subgroups were compared, and then the patient means and SDs of the two groups were compared.

Table 1.
Group Metrics for Central Tendency and Variability of Blood Glucose

	Entire cohort	Lower-variability subgroup[a]	Higher-variability subgroup[a]
Number of patients	20	10	10
Number of BG results	1032	527	505
(1a) Metrics from untransformed overall BG data (*n* = number of BG results)			
Overall mean in mg/dl	109	105	113
(±overall SD in mg/dl)	(±28)	(±17)	(±35)
Interval bounds in mg/dl, ± 1 SD	(82–137)	(88–123)	(78–148)
Interval bounds in mg/dl, ± 2 SDs	(54–164)	(71–140)	(43–183)
(1b) Distribution of BGs			
Number of BG within mean ± 1 SD[b]	814 (78.9%)	384 (72.9%)	394 (78.0%)
Number of BG within mean ± 2 SDs[b]	986 (95.5%)	499 (94.7%)	486 (96.2%)
(2) Metrics from untransformed BGs of each patient in mg/dl (*n* = number of patients)			
Mean of BG means of each patient	109	106	113
Mean of SDs of each patient	24	16	32
(3a) Reverse-transformed metrics from logarithmically transformed overall BG data (*n* = number of BG results)			
Overall mean BG in mg/dl	106	104[c]	108[c]
(÷/× overall MSD)	(÷/× 1.26)	(÷/× 1.18)	(÷ /× 1.33)
Interval bounds in mg/dl within first MSD	(84–134)	(88–123)	(82–144)
Interval bounds in mg/dl within second MSD	(67–168)	(74–145)	(62–191)
(3b) Distribution of BGs			
Number of BG within first MSD[b]	788 (76.4%)	384 (72.9%)	370 (73.3%)
Number of BG within second MSD[b]	975 (94.5%)	499 (94.7%)	480 (95.0%)
(4a) Reverse-transformed metrics from logarithmically transformed BG data of each patient (*n* = number of patients)			
GGM in mg/dl	106	104	109
(÷/× 1 MSD of GGM)	(÷/× 1.07)	(÷/× 1.07)	(÷/× 1.07)
MSSD	1.24	1.17[d]	1.31[d]
(÷/× 1 MSD of MSSD)	(÷/× 1.07)	(÷/× 1.03)	(÷/× 1.05)
GGM in mg/dl, ÷/× MSSD once	(86–132)	(89–122)	(83–142)
GGM in mg/dl, ÷/× MSSD twice	(70–163)	(76–142)	(64–186)
(4b) Distribution of BGs			
Number of BG within 1 MSSD of GGM[b]	754 (73.1%)	360 (68.3%)	360 (71.3%)
Number of BG within 2 MSSDs of GGM[b]	959 (92.9%)	491 (93.2%)	478 (94.7%)

[a] The SDs of the logarithmically transformed BG data sets were rank ordered, and the patient members of the cohort were divided into lower and upper halves (see text).
[b] The actual counts of BG results from the sampled groups are given.
[c] $p = .0027$.
[d] $p < .00004$.

Results

The frequency distribution of BG values is shown for the overall BG values of each of the two groups of 10 patients in **Figure 2**. The results of four methods of analysis of each group are shown in **Table 1** for the entire cohort and for the lower- and higher-variability patient subgroups. In methods 3 and 4, the initial logarithmic transformation converts the data into the form used for development of means and SDs and for statistical testing, after which, in each method, the means and interval bounds are reverse transformed monotonically to yield the results shown.

When the patient subgroups with lower and higher variability were compared with respect to their logarithmically transformed overall BG data sets, consisting of 527 measurements from the lower-variability subgroup and 505 measurements from the higher-variability subgroup of patients, the mean overall value of the logarithmically transformed BG of the two subgroups differed ($p = .0027$). In method 3, the overall means ± SD of the logarithmically transformed BGs for the lower- and higher-variability sub-groups were 0.760562663 ± 0.072367226 versus 0.779476971 ± 0.122302184, respectively, which are reverse transformed to geometric means and MSDs of 104 (÷/× 1.18) versus 108 (÷/× 1.33) mg/dl. When the 10 means and 10 SDs from the logarithmically transformed BG data sets of all patients within each of the two subgroups were compared, the means of the means did not differ ($p = .16$), but the means of the SDs differed ($p < .00004$). After reverse transformation, the GGMs with MSD were 104 (÷/× 1.07) versus 109 (÷/× 1.07) mg/dl for the patient groups having the lower and higher variability, respectively. Expressed in unitless numbers, the corresponding MSSDs with MSDs were 1.17 (÷/× 1.03) versus 1.31 (÷/× 1.05) mg/dl. Under methods 1, 3, and 4, the actual counts and percentage of BG results from the sampled groups that fell within the range of interval bounds are stated for comparison with the statistical prediction for the population. For each of the two groups of 10 patients, the percentage of overall BG values for the entire group that fell within interval bounds is shown graphically for methods 1–4 in **Figure 3**.

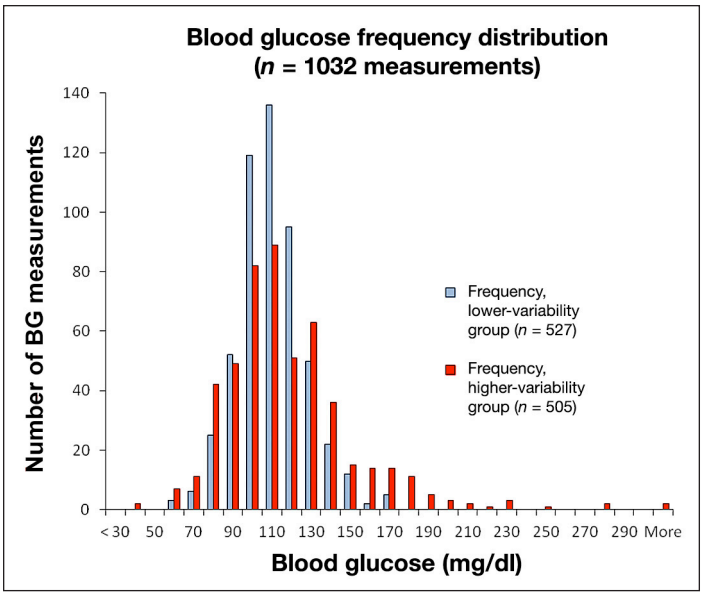

Figure 2. The overall frequency distribution for each of two patient groups ($n = 10$ in each group) described in the text is shown as the number of BG measurements falling within bins of BG concentration incrementally increasing from left to right by 10 mg/dl between markers.

Discussion

The performance of several metrics for evaluation of glycemic variability in the hospital has been reviewed.[6] Here we are focusing on proposed improvements to the use of SD as a variability metric. First, it is important to ensure stability of a measure of central tendency during the time of observation if SD is intended to reflect variability. Second, in this discussion, we address a solution to the problem of the distribution of BG, which characteristically requires transformation for appropriate use of SD for descriptive purposes or performance of parametric statistical comparisons. Third, we focus on the importance of using the patient as the unit of observation for BG metrics, rather than the BG.

The authors do not advocate either of the approaches 1 or 2 shown in **Table 1** but display the results for comparison, recognizing that historically important publications on the subject of glycemic variability have used untransformed raw BG data. Although glycemic variability was not the principal focus of the article, the first method, using BG as the unit of observation, was employed in the Leuven, Belgium, 2001 trial of intensive glycemic control in the surgical intensive care unit.[12] The second method of analysis was used by two pivotal observational reports about the interaction between glycemic variability and outcomes.[1,2] By using the raw data of the patient as the unit of observation, it was possible to correlate SD with individual outcomes.

Reverse transformation will monotonically preserve the order of BG values and the values of the interval bounds. As is true in general for MSD for positively skewed data, after reverse transformation, the interval bounds are asymmetric about the measure of central tendency, with a wider range above than below. For an excellent visual depiction, the reader is directed to two-panel Figure 3 in the paper by Limpert and coauthors,[11] which shows the distribution of idealized hypothetical data drawn as a continuous curve. The effect of transformation is to compress the long right-hand end of the curve so that the peak of the redrawn curve after logarithmic transformation is centered on the mean of the transformed data. In the present study, as is true in general for geometric means of positively skewed data, in comparison with arithmetic means, the reverse-transformed metrics for central tendency shown in methods 3 and 4 are lower than the arithmetic means shown in methods 1 and 2. The positive skew of untransformed BG data is more apparent in the group having higher variability (**Figure 2**).

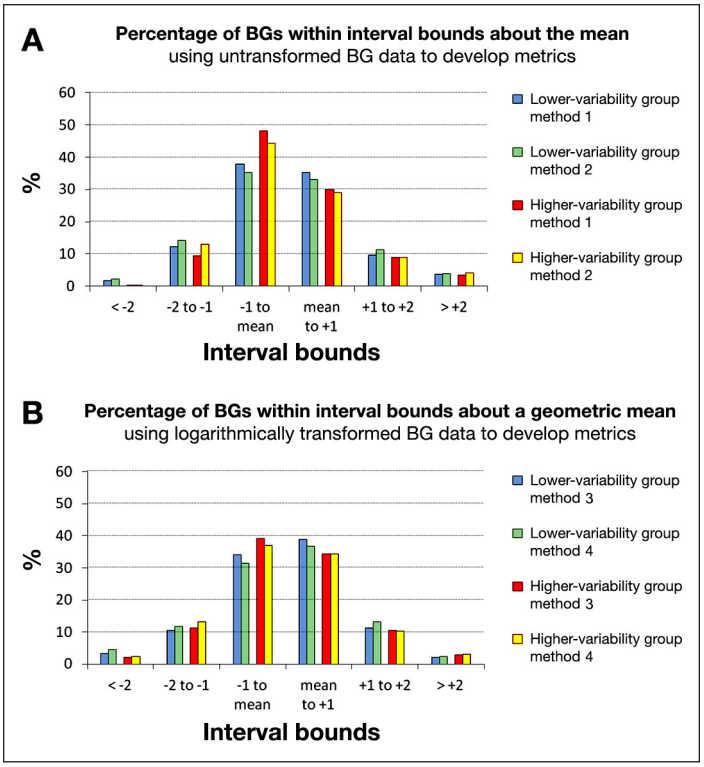

Figure 3. Interval bounds are established under each of four methods with reference to the following metrics: the mean and SD using untransformed overall BG data (method 1); the mean of BG means and the mean of SDs of each patient, using untransformed BGs of each patient (method 2); the overall geometric mean and MSD using reverse-transformed metrics from logarithmically transformed overall BG data (method 3); and the reverse-transformed mean of means (GGM) and mean of SDs (MSSD) of logarithmically transformed BG data of each patient (method 4). Interval bounds (<-2; -2 to -1; -1 to mean; mean to +1; +1 to +2; and >+2) refer to **(A)** values obtained by use of a mean and an arithmetic SD **(B)** or a geometric mean and MSD to define ranges bounded by BG values. The interval bounds in methods 1 and 2 equal mean ±1 or ±2 SDs. The interval bounds in method 3 equal geometric mean (÷/× MSD) or geometric mean (÷/× MSD^2). The interval bounds in method 4 equal GGM (÷/× MSSD) or (÷/× $MSSD^2$). To determine the percentage of BG measurements falling within interval bounds, each of the four methods of metrics for central tendency and variability is applied to the overall BG data of two patient groups described in the text (n = 10 patients in each group, having lower and higher variability) to determine percentage of BGs (n = 527 and 505 BG measurements in the lower- and higher-variability groups, respectively) within the interval bounds defined under each method.

Reverse-transformed metrics may improve the predictive credibility of the interval bounds for overall group BG data. In the present study, under methods 3 and 4, the mean and SD of logarithmically transformed BG data were used to establish interval bounds. Compared with use of metrics based on untransformed data under methods 1 and 2, the improvement of symmetry of BG measurements about the mean and the actual percentage distribution of BG measurements between the values demarcated by the mean and first and second interval bounds suggest that the distribution of the logarithmically transformed BGs has approached a normal distribution (**Figure 3**).

A limitation of the method of use of logarithmic transformation, reverse transformation, and MSD is the effect of rounding . The final results here are expressed to two decimal places for the MSD and none for BG in milligrams/deciliters. A limitation of the present study is that it has not been convincingly demonstrated from a large sample of patients whether the collection of means or SDs of transformed BGs of each patient would yield a normal distribution of these means or SDs. In case future evaluation shows deviation from a normal distribution, nonparametric testing could be used to compare distributions of these means or SDs.

From the complete data set of the cohort of intensive care unit patients published by Chase and coauthors,[9] the reported overall glycemic average of reverse-transformed BG data was 105 mg/dl, with a first MSD of 1.2x, yielding a predicted 66% 1-SD range of 86–126 mg/dl and a 95% 2-SD range of 72–151 mg/dl. Using method 3 in **Table 1**, we performed a similar analysis of overall results for the same cohort, using logarithmically transformed BGs but restricting the data to the first 72 h of treatment. The overall mean BG after reverse transformation was 106.1 mg/dl with a 1-SD range of 84.2–133.6 mg/dl and a 2-SD range of 66.8–168.4 mg/dl.

Taken together, in method 4 the GGM and MSSD describe an artificial patient who may be seen as a typical member of a group. The choice of the term "artificial" results from the use of a surrogate value for the MSSD and the creation of a GGM, which is actually a reverse-transformed mean of means. The principal advantage of method 4 is that the status of individual patients according to variability becomes evaluable. Going forward, in the field of glycemic control, we need to become sensitized to recognizing ranges of MSD values that are low or high, without mentally applying them to a mean BG. However, the reverse transformation permits expression of the GGM and interval bounds in familiar units of measure. The MSSD and GGM are not mathematically linked in the same obligatory manner as a true SD is linked to the distribution of BGs associated with its mean. It cannot be predicted that 68% of measurements from the randomly sampled population will fall within 1 MSSD of the GGM or 95% within 2 MSSDs of the GGM. If all patients in the population had the statistics of the BG distribution described for the artificial patient (or if there was only one patient), then 68% of BG values overall for the population would fall within the first interval bounds and 95% within the second interval bounds.

Use of parametric testing dependent upon mean and SD for group comparisons requires that each group have an approximately normal distribution. Differences between groups in the protocol-controlled population reported here were not demonstrable prior to logarithmic transformation of data. After logarithmic transformation of BGs, using method 4, it was possible to confirm a difference of variability between two subgroups of 10 patients each. A difference of the overall mean BG was demonstrable statistically only when using method 3 to compare the 527 versus 505 overall BG values of the two groups.

The demonstration data patient group was tightly controlled under the SPRINT protocol, having a single target range.[13] One might envision a different situation in which algorithm designs or institutional protocols were capable of aiming at more than one target range, having, for example, one default target range for general critical care and a second target range for diabetic ketoacidosis.[14,15] The overall BG distribution after reaching target range control might then exhibit a bimodal pattern, with overall mean intermediate between the two targets. Ideally, the mean BG values for each patient would cluster into the differing target ranges appropriate to the conditions of the patients. The overall SD of BGs considered collectively for the group might overestimate the variability experienced by individual patients. The SD for the BG of each patient then need not be a high value but might be proportionate to the mean BG achieved, probably with similar coefficient of variability between patients. These two theoretical examples—(a) tight control of central tendency despite differences of individual variability and (b) differences of central tendency despite tight control of individual variability—are used to emphasize the potential importance of patient-level determination of group metrics for central tendency and variability.

It is proposed that the GGM may be used to study the relationship of overall glycemia to outcomes and also the effectiveness of algorithms in achieving desired targets for groups or subgroups of patients. The GGM describes the central tendency characteristic of patient members of a group and, although the GGM entails logarithmic transformation as an initial step, by reverse transformation, GGM expresses the central tendency metric in units familiar to the reader.

There is a need to examine the impact of variability upon the outcomes of individual patients. In order to do so, a metric is required by which the variability of a patient can be compared with the typical variability that is characteristic of a patient member of his or her group. In particular, as variability is associated with individual patient outcomes, there is a need to present patient-specific variability metrics but also, as presented here, to group those metrics in a concise and useful way in presenting and analyzing larger studies. We propose that the MSSD is a candidate metric that may be used to describe the typical variability of an individual group or subgroup member for study of relationship of patient variability to outcomes.

Future research should seek to evaluate variability as a predictor of outcomes, independent of hypoglycemia or severe hyperglycemia. Assuming prevention of hypoglycemia can be achieved, it may be argued that we do not know the relative burden of medical strategies that might minimize variability, as compared with any burden resulting from glycemic variability itself. Improvements in insulin algorithms and the development of non-insulin-based strategies may permit future studies to be conducted that may randomize patients to greater or lesser glycemic variability

without significant severe differences in hypoglycemia or overall hyperglycemia. The proposed metrics GGM and MSSD have been developed and validated in a very small set of patients. Evaluation will be required eventually to examine the ability of GGM and MSSD, compared with other metrics for variability and central tendency, to predict nonglycemic outcomes.

Conclusions

The GGM and MSSD are presented as group metrics, requiring logarithmic transformation of the BG data set of each patient. Development of statistics before a final reverse transformation permits identification of predictive interval bounds and application of statistical testing for group comparisons.

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