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Glucose Variability: Comparison of Different Indices During Continuous Glucose Monitoring in Diabetic Patients

Jean-Pierre Le Floch, MD[1] and Laurence Kessler, MD, PhD[2]

Abstract

Background: Glucose variability has been suspected to be a major factor of diabetic complications. Several indices have been proposed for measuring glucose variability, but their interest remains discussed. Our aim was to compare different indices.

Methods: Glucose variability was studied in 150 insulin-treated diabetic patients (46% men, 42% type 1 diabetes, age 52 ± 11 years) using a continuous glucose monitoring system (668 ± 564 glucose values; mean glucose value 173 ± 38 mg/dL). Results from the mean, the median, different indices (SD, MAGE, MAG, glucose fluctuation index (GFI), and percentages of low [<60 mg/dL] and high [>180 mg/dL] glucose values), and ratios (CV = SD/m, MAGE/m, MAG/m, and GCF = GFI/m) were compared using Pearson linear correlations and a multivariate principal component analysis (PCA).

Results: CV, MAGE/m (ns), GCF and GFI ($P < .05$), MAG and MAG/m ($P < .01$) were not strongly correlated with the mean. The percentage of high glucose values was mainly correlated with indices. The percentage of low glucose values was mainly correlated with ratios. PCA showed 3 main axes; the first was associated with descriptive data (mean, SD, CV, MAGE, MAGE/m, and percentage of high glucose values); the second with ratios MAG/m and GCF and with the percentage of low glucose values; and the third with MAG, GFI, and the percentage of high glucose values.

Conclusions: Indices and ratios provide complementary pieces of information associated with high and low glucose values, respectively. The pairs MAG+MAG/m and GFI+GCF appear to be the most reliable markers of glucose variability in diabetic patients.

Keywords

continuous glucose monitoring, glucose fluctuation index, glucose variability, MAG, MAGE

Glucose variability is a recurrent theme addressed in diabetic publications.[1,2] It has been suspected to be a major factor of diabetic complications, especially in type 2 diabetes, in experimental conditions and in patients in intensive care units.[3-8] A high degree of glycemic excursions is expected to be more detrimental than sustained hyperglycemia, although this has not been consistently observed, notably in type 1 diabetes and in retrospective analyses of cohort studies.[9-15] In addition, no randomized, prospective study has supported the link between glucose variability and degenerative complications. Then, the association remains to be discussed. However, indices of glucose variability could be especially useful to analyze ambulatory glucose profiles and optimize decision making in diabetes.[16] For the clinician, it is important to get simple indices, poorly dependent of the mean glucose value commonly estimated with HbA1c and associated with glucose fluctuations both in high and low glucose values.

Numerous methods have been proposed for measuring glycemic variability, including the classical standard deviation (SD), the mean amplitude of glucose excursion (MAGE), the mean absolute difference of consecutive glucose values (MAD), the mean absolute glucose change (MAG), the continuous overall net glycemic action (CONGA), low and high blood glucose indices (LBGI-HBGI), and the glycemic risk assessment diabetes equation (GRADE).[17-24] Nonparametric median and interquartile range (IQR) have also been proposed, as well as the multiplicative standard deviation (MSD)

[1]Diabetology, Clinique de Villecresnes, Villecresnes, France
[2]Diabetology, CHRU de Strasbourg, Strasbourg, France

Corresponding Author:
Jean-Pierre Le Floch, Diabetology, Clinique de Villecresnes, 8 Bd Richerand, 94440 Villecresnes, France.
Email: jplefloch@dietvill.com

of the geometric mean, and a qualitative description of glucose fluctuations using the Poincaré plot.[25-27] However, none has proven to be the gold standard marker of glycemic variability, and their respective benefits remain controversial.[1,2,28] Finally, the urinary assay of 1,5-anhydroglucitol has been proposed, but its measurement remains difficult.[29] In this study, we used also 2 new markers of glucose variability based on consecutive glucose differences: the glucose fluctuation index (GFI), and its ratio to the mean of glucose values, the glucose coefficient of fluctuation (GCF). We compared the results obtained with different indices of glucose variability, using a continuous glucose monitoring system in diabetic patients.

Methods

Glycemic fluctuations were studied in 150 diabetic patients, 63 (42%) with type 1 and 87 with type 2 diabetes. Of these, 69 were men (46%) and 81 women, aged 52 ± 11 years, and with a mean duration of diabetes of 12 ± 5 years. All the patients were being treated with insulin, using multiple injections or insulin pumps (n = 17; 11%).

Glucose values were recorded every 5 minutes using a continuous glucose monitoring system (CGMS) over a period of at least 24 hours. The numbers and types of CGMS used were 26 G4, 42 G5 (Dexcom, San Diego, Ca, USA), 38 I Pro (Medtronic, Minneapolis, MN, USA), and 44 Navigator 2 (Abbott Medical Care, Lake Forest, IL, USA). Missing values were not replaced. The same set of data was used for each patient in the calculations of the various indices and ratios.

Indices and Ratios of Glucose Variability

Calculations were made for each patient of the mean, SD, coefficient of variation (CV, defined as the ratio of SD to the mean), the median, IQR, and the ratio of IQR to median (IQR/med). The percentages of low glucose values (LGV) (<60 mg/dL [3.3 mmol/L]) and of high glucose values (HGV) (>180 mg/dL [10 mmol/L]) were defined. MAGE was computed by the same operator, using an automated procedure.[18] Increasing and decreasing excursions > 1 SD were identified. The MAGE was then computed as the mean of either increasing or decreasing excursions, depending on the first significant excursion. The MAGE to mean ratio (MAGE/m) was defined. The MAG was calculated as the mean of the absolute differences between consecutive glucose values. The MAG to mean ratio (MAG/m) was defined. GFI was the square root of the mean of squared consecutive glucose differences:

$$\mathrm{GFI} = \sqrt{\frac{\sum_{i=1}^{(n=1)} (G_i - G_{i+1})^2}{(n-1)}}$$

GCF was the ratio of GFI to the mean of glucose values. All ratios were expressed in percentages.

Table 1. Indices of Glucose Variability and Correlations With Mean Glucose Value.

	Mean ± SD	Correlation (R^2)	Slope	Constant	*P* value
SD (mg/dL)	58.8 ± 19.5	.35	0.299	7.15	<.0001
CV (%)	34.1 ± 9.0	.01	–0.011	36.1	.555
IQR (mg/dL)	82.9 ± 32.3	.35	0.496	–2.86	<.0001
IQR/med (%)	50.4 ± 16.6	.01	0.070	49.2	.846
MAGE (mg/dL)	104.9 ± 39.0	.29	0.541	11.4	<.0001
MAGE/m (%)	60.8 ± 18.8	.01	–0.014	63.2	.736
MAG (mg/dL)	5.4 ± 2.3	.06	0.015	2.83	.003
MAG/m (%)	3.2 ± 1.4	.06	–0.009	4.66	.003
GFI (mg/dL)	8.8 ± 4.6	.03	0.022	4.95	.022
GCF (%)	5.3 ± 2.7	.03	–0.013	7.45	.025
HGV (%)	38.8 ± 22.3	.91	0.554	–56.9	<.0001
LGV (%)	1.5 ± 2.6	.15	–0.027	6.09	<.0001

Statistical Analyses

Descriptive values are presented as mean ± SD or percent. Fourteen variables, including 7 indices and 5 ratios, were studied: the mean, SD and CV, the median, IQR and IQR/med, the percentages of LGV and HGV, the MAGE and MAGE/m, the MAG and MAG/m, the GFI and GCF. Correlations between variables were performed using Pearson's linear regression.

To compare the information derived from the various indices and ratios of glycemic variability, a multivariate principal component analysis (PCA) was performed after normalization (centralization and reduction) of each variable, using the correlation method.[30] The mean, median, 7 indices and 5 ratios were associated with the axes on which they showed their higher eigenvalues.

Results

On average, 668 ± 564 glucose values were recorded using CGM in the 150 patients under study; 3% of the individual data were missing and were not replaced in the calculations. The mean glucose value was 173 ± 38 mg/dL. The median glucose value was 166 ± 41 mg/dL. Mean values and SD of the different indices and ratios are presented in Table 1.

Correlations With the Mean (Table 1)

Nonsignificant or slight correlations were observed between the mean of glucose values and the CV, IQR/med, MAGE/m (NS) GCF and GFI ($P < .05$), MAG and MAG/m ($P < .01$), suggesting relative independence of these variables on the mean value (percentage of variance explained R^2 <0.10; Table 1). Conversely, strong correlations ($R^2 \geq .10$, $P < .001$) were observed between the mean and the SD, IQR, MAGE, and percentages of HGV and LGV (Table 1).

Similar results were found with the median.

Table 2. Correlations Between Indices and Ratios of Glucose Variability and the Percentages of HGV and LGV.

	HGV (%)				LGV (%)			
	Correlation (R^2)	Slope	Constant	*P* value	Correlation (R^2)	Slope	Constant	*P* value
SD (mg/dL)	.30	0.478	40.2	<.0001	.01	0.423	58.1	.485
CV (mg/dL)	.01	–0.020	34.9	.539	.20	1.531	31.9	<.0001
IQR (mg/dL)	.30	0.795	52.0	<.0001	.01	–0.063	83.0	.950
IQR/med (mg/dL)	.01	0.005	50.2	.937	.09	1.911	47.6	.0001
MAGE (mg/dL)	.25	0.879	70.8	<.0001	.01	–0.025	104.9	.998
MAGE/m (mg/dL)	.01	–0.018	61.5	.795	.10	2.231	57.5	<.0001
MAG (mg/dL)	.05	0.023	4.44	.006	.01	0.022	5.32	.759
MAG/m (mg/dL)	.06	–0.015	3.75	.003	.07	0.134	2.97	.001
GFI (mg/dL)	.03	0.038	7.35	.024	.01	0.098	8.69	.496
GCF (mg/dL)	.03	–0.022	6.11	.026	.06	0.242	4.91	.003

Correlations With HGV

Strong correlations were observed with SD, IQR and MAGE ($R^2 \geq .10$, $P < .001$; Table 2). Significant but weak correlations ($R^2 < .10$, $P < .05$) were found with MAG, MAG/m, GFI and GCF, whereas CV, IQR/med, MAGE/m were not significantly correlated with HGV (Table 2).

Correlations With Hypoglycemia

A strong correlation was observed with CV, IQR/med, and MAGE/m ($R^2 \geq .10$, $P < .001$; Table 2). Significant correlations ($R^2 > .05$, $P < .01$) were found with MAG/m and GCF. The other indices and ratios were not significantly correlated with the percentage of LGV (Table 2).

Correlations of Indices and Ratios

GFI was strongly correlated with SD ($R^2 = .17$, $P < .001$), CV ($R^2 = .13$, $P < .001$), MAGE ($R^2 = .12$, $P < .001$), MAG/m ($R^2 = .17$, $P < .001$), and especially with MAG ($R^2 = .67$, $P < .001$) and GCF (0.79, $P < .001$). It correlates somewhat less so with IQR ($R^2 = .05$, $P < .01$), IQR/med ($R^2 = .04$, $P < .05$), and MAGE/m ($R^2 = .08$, $P < .001$).

GCF was strongly correlated with CV ($R^2 = .14$, $P < .001$) and very strongly with MAG ($R^2 = .61$, $P < .001$) and MAG/m ($R^2 = .81$, $P < .001$), but somewhat less so with SD ($R^2 = .04$, $P < .05$), IQR/med ($R^2 = .04$, $P < .05$), and MAGE/m ($R^2 = .08$, $P < .001$). It was not significantly correlated with IQR ($R^2 = .01$, ns) or MAGE ($R^2 = .02$, ns).

PCA

Using PCA, 3 main axes were found, each accounting for >15% of variance, for a total of 85% of variance explained (Table 3). Axes 4 and 5 accounted for 5.5% and 4.8% of variance, respectively. Additional axes accounted for less than 2% of variance.

The first axis (>39% of variance explained) was the main axis for the mean, SD, CV, median, IQR, IQR/med, MAGE, MAGE/m and the percentage of HGV (Table 3). On the second axis (>28% of variance), MAG/m, GCF, and the percentage of LGV showed their highest eigenvalues. CV was also associated with this axis, but with a lower value than that observed on the first axis (Table 3). The third axis was the main axis for MAG and GFI. Both were also associated with the first axis, but with a lower eigenvalue. The percentage of HGV was present on this third axis but showed an eigenvalue slightly lower than that found on the first axis. Ratios MAG/m and GCF had lower values than on the second axis (Table 3). Secondary axes 4 and 5 were mainly associated with the nonparametric IQR and IQR/med, and with LGV, respectively.

Finally, the first axis appeared to be associated with descriptive information, such as the mean, SD, CV (or nonparametric median, IQR and IQR/med), the percentage of HGV, the MAGE, and its ratio to the mean. The second axis dealt with ratios of glucose variability (MAG/m, GCF, and CV) and the percentage of LGV. The third axis was that of MAG, GFI, and the percentage of HGV.

Discussion

In this study, we compared different indices and ratios of glucose variability. We concluded on the interest of using both an index and its ratio to the mean, especially the pairs MAG+MAG/m or GFI+GCF.

A large sample of patients was observed, including patients with both type 1 and type 2 diabetes, which have previously shown discordant results.[6,14,15,17,31-33] Glucose values were obtained every 5 minutes for each patient using different kinds of CGMS over at least 24 hours.[34] A large number of values were then recorded and computed to calculate all the indices and ratios under study. The mean, median, indices, and ratios were then compared using the same sample of data. Therefore, individual characteristics of patients did not influence our results.

In this study, we proposed a new index of glucose variability, the GFI, and its ratio to the mean, the GCF. The GFI

Table 3. Principal Component Analysis: Eigenvalues of Mean, Median, Indices, and Ratios of Glucose Variability.

	Axis 1 (39.3 %)[a]	Axis 2 (67.5%)[a]	Axis 3 (84.9%)[a]	Axis 4 (90.4%)[a]	Axis 5 (95.2%)[a]
Mean	**0.23**	–0.39	*0.19*	0.04	0.12
SD	**0.39**	–0.10	–0.12	*0.16*	–0.04
CV	**0.31**	*0.20*	–0.30	0.17	–0.03
Median	**0.20**	–0.41	*0.20*	0.01	0.24
IQR	**0.35**	–0.16	–0.18	*0.29*	–0.14
IQR/med	*0.29*	0.11	–0.35	**0.35**	–0.24
MAGE	**0.36**	–0.10	–0.12	–0.53	–0.01
MAGE/m	**0.27**	0.15	–0.26	–0.66	0.01
MAG	*0.27*	0.18	**0.40**	0.06	–0.01
MAG/m	0.16	**0.38**	*0.31*	0.04	0.01
GFI	*0.27*	0.20	**0.37**	–0.01	–0.02
GCF	0.19	**0.36**	*0.31*	0.01	–0.01
HGV	**0.22**	–0.38	*0.18*	0.04	*0.21*
LGV	0.05	**0.27**	–0.24	0.13	**0.90**

Values in bold indicate the axis with the higher eigenvalue for the variable. Values in italics indicate the secondary axis.
[a]Cumulative percentage of variance explained.

is based on consecutive glucose differences. But, in contrast to MAG, which averages absolute consecutive glucose differences, the consecutive differences in GFI are squared prior to finding their mean and taking the square root. The potential benefit is that differences are weighted individually, giving more importance to the greatest ones, which are likely to be more detrimental. Compared to SD, the GFI and the MAG are based on consecutive glucose differences instead of differences of glucose values to the mean. Therefore, they are indices of glucose variability, whereas SD is an index of dispersion of the glucose values, in which the order of occurrence is not important.[2, 8,11,12] GFI formula is similar to that of SD, where the sum of squared differences of consecutive glucose values replaces the sum of squared differences of glucose values to the mean. From a statistical point of view, the GFI can be seen as a root-mean-square successive difference, which has been used previously in heart rate variability.[35,36]

The GCF is the ratio of the GFI to the mean, similar to the relationship in which CV is the ratio of SD to the mean. In our study, other ratios to the mean were defined, especially for the MAGE (MAGE/m) and the MAG (MAG/m), or to the median for the IQR (IQR/med). The potential value of this approach is to obtain markers of variability that are relatively independent of the mean (median), a hypothesis which was confirmed by our results showing poor correlations between the mean (median) and the ratios. Ratios appear thus to be complementary of genuine indices, which are usually dependent on the mean (or median), a result that was also confirmed by our study. This complementarity suggests that both the indices and their ratios should be used simultaneously.

Not all the indices of glucose variability were used and compared. These include the CONGA, SDhh:mm, glucose fluctuation, and the median change in hourly glucose median, which show similarities to the GFI.[13,19,22,37-39] Further studies are then required to compare these indices to GFI and MAG, and to find their relative benefits and limitations.

Another limitation is that with the use of MAG or GFI, missing data cannot be replaced without bias. Averaging the previous and the following glucose values, or using the LOCF (least observation carried forward) method, commonly performed in ANOVA, would bias the indices. The percentage of missing data appears therefore to be an important piece of information about the quality of the data set, especially when comparing different records.

Nonparametric indices and ratios were used in our study (median, IQR, IQR/med). They provided similar information as that found using the mean, SD, and CV, and did not show a clear benefit in the estimation of glucose variability. They were just found isolated on the fourth axis of the PCA for 5% of variance explained. Nonparametric indices, such as IQR, as well as the logarithmic transformation leading to geometric mean and MSD with reverse transformation of the presented data, or the qualitative description of values using the Poincaré Plot, aim to deal with the non-Gaussian distribution of the glucose values.[2,19,25-27] Although these approaches are complex, they could be useful for dealing with small samples of data.

Good indices of glucose variability should not be strongly associated with the mean glucose value (or the median). SD, IQR, and MAGE showed strong correlations with the mean, which have been reported previously.[19] Thus, they did not appear to be pertinent markers of glucose variability.

Because hyperglycemia, especially postprandial, is an important factor of glucose variability, good glucose variability markers should be associated with HGV. In our study, the indices, such as SD, IQR, MAGE, and accessorily MAG, GFI, and their ratios MAG/m and GCF showed an association with

the percentage of HGV. Similarly, because hypoglycemia is also an important factor of glucose variability, good glucose variability markers should be associated with LGV. Significant correlations of the percentage of LGV were found mainly with the ratios CV and MAGE/m ($R^2 \geq .10$), and accessorily ($R^2 > .05$) with IQR/med, MAG/m, and GCF.

Because multiple comparisons were conducted using the bivariate correlations, significant results can be observed due to the number of tests performed.[37] Multivariate analysis could therefore help to clarify this. In our study, for the first time, a multivariate PCA was used. PCA aimed to reduce the size of the initial cloud of information (14 axes and dimensions) to better understand the relationships between the 14 variables under study.[30] It performed repeated correlations, each leading to an axis and to residuals, on which a new correlation was performed to get a new perpendicular axis and new residuals, and so on, until all the variance was explained and a new set of 14 axes was obtained. All the variables studied were normalized (centered so that the mean becomes 0 and reduced so that the variance becomes 1) prior to computations to avoid size effects of units. Each eigenvector of each of the 14 variables was projected on the new set of axes and characterized by its eigenvalue. The closer the eigenvalue is to 1, the closer the eigenvector of the variable is to the axis.

Three main axes explained most (85%) of the variance of the initial cloud. The first axis dealt mainly with descriptive information: mean, median, SD, CV, IQR, IQR/med. The percentage of HGV was also found on this axis, not surprisingly because it is associated with the mean and with the dispersion of the glucose values. Less expected were the MAGE and its ratio, MAGE/m. MAGE was previously reported to be strongly associated with the mean and moreover the SD, as in our study.[19] This suggests that MAGE could be associated with the dispersion, more than with the variability of the glucose values. Therefore, its value as a marker of glucose variability may be controversial.

The second axis associated ratios (MAG/m, GCF, and CV) with LGV. The association with hypoglycemia had been reported previously for CV,[2,28] but in our study the ratios of glucose variability, MAG/m, and GCF were most strongly associated with the frequency of LGV.

The third axis associated 2 indices of glucose variability, MAG and GFI (more than their ratios), and the percentage of HGV.

Minor axes 4 and 5, which accounted for only about 5% of variance, could describe specific phenomena, for instance nonparametric dispersion and hypoglycemia without variability (without rebound).

Finally, the first axis appeared to be associated with descriptive information, mainly dependent on the mean (or nonparametric median). Indices on this axis (SD, IQR, MAGE) did not seem very useful for estimating glucose variability. The second axis dealt with the percentage of LGV. Ratios on this axis (MAG/m, GCF, and CV) and could be considered as useful markers of glucose variability. Similarly, the third axis, which was associated with the percentage of HGV, include useful markers of glucose variability in this area, the MAG and GFI. Therefore, for the clinician, it may be useful to use pairs (index + ratio) simultaneously. Of the different pairs, PCA suggests that MAG+MAG/m and GFI+GCF are the most reliable markers of glucose variability. As reported previously,[1,2] the MAGE+MAGE/m pair seems to be less useful.

Hypoglycemia however has not been fully explained by these pairs. In our study, it appears as an isolated factor on the fifth axis of the PCA. This could be due to the poor weight and influence of LGV on the calculation of the indices. In addition, only hypoglycemia followed by a rebound can induce significant glucose differences and variability. Therefore, the percentage of LGV should be included in the descriptive information.

Our results do not suggest superiority of either of the pairs of MAG+MAG/m or GFI+GCF. Both pairs were very strongly correlated and provided very similar information, probably due to the fact that they are similarly computed using consecutive glucose differences.

The clinical interest of our new indices GFI and GCF remains uncertain. Studies have suggested that acute glucose variations are likely to have an impact of long term diabetic complications, and therefore that indices of glycemic variability should be included in the assessment of glucose control in diabetic patients.[13,40] Excessive protein glycation and activation of the oxidative stress can be involved. However, this remains discussed and further studies are required to specify the interest of using indices of glycemic variability derived from CGM in the long term management of glucose control in diabetic patients.[7,8,10] This is especially true for our new indices, GFI and GCF. An other interesting approach is to consider the long term glycemic variability estimated using HbA1c. A recent meta-analysis suggest an association between HbA1c variability (SD or CV) and both micro- and macrovascular complications of diabetes.[41] Here too, more specific indices of variability, such as MAG, GFI, or their ratios may be useful.

Conclusions

Indices and ratios provide complementary pieces of information associated with the percentages of high and low glucose values, respectively; therefore glucose variability could be usefully estimated using pairs of indices, such as MAG+MAG/m and/or GFI+GCF. MAGE appears to be less useful.

Abbreviations

CGM, continuous glucose monitoring; CONGA, continuous overall net glycemic action; CV, coefficient of variation; GCF, glucose coefficient of fluctuation; GFI, glucose fluctuation index; m, mean; GRADE, glycemic risk assessment diabetes equation; HGV, high

glucose values; IQR, interquartile range; LGV, low glucose values; MAG, mean absolute glucose change; MAGE, mean amplitude of glucose excursions; med, median; MSD, multiplicative standard deviation; PCA, principal component analysis; SD, standard deviation

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