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Group of Signs: A New Method to Evaluate Glycemic Variability

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Abstract

Background:

Glycemic variability is an important parameter used to resolve potential clinical problems in diabetic patients. It is known that glycemic variability generates oxidative stress and potentially contributes to the development of macro- and microvascular complications in diabetes. By controlling glycemic variability, it is possible to reduce these complications and to set the therapy for all patients with diabetes. The aims of this study were to (1) propose a new standardized, objective, and flexible approach to measure glycemic variability by a continuous glucose monitoring system (CGMS)—the group of signs (GOS) method; (2) compare the correlation between mean amplitude of glucose excursion (MAGE), a well-known index of glycemic variability calculated by the physician and the MAGE defined with the GOS method, in order to validate the GOS; and (3) suggest new indexes of glycemic variability.

Methods:

We tested the GOS algorithm on data collected by a CGMS every 5 minutes for 24 hours on 50 patients. Consequently, for 8 patients we calculated and compared the physician's MAGE in the standard way and by the GOS method.

Results:

Comparison between the two methods has shown high correlations, from a minimum correlation of 86% to a maximum of 98%, with p values <0.01 (Pearson test).

Conclusions:

Preliminary data suggest that the proposed algorithm is a valid, efficient, and reliable method able to calculate the standard MAGE on CGMS data systematically and to create other alternative glycemic variability indexes.

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Abbreviations: (BG) blood glucose, (CGMS) continuous glucose monitoring system, (DCCT) Diabetes Control and Complications Trial, (FPG) fasting plasma glucose, (GOS) group of signs, (HbA1c) hemoglobin A1c, (iso-$PGF_{2\alpha}$) 8-iso-prostaglandin $F_{2\alpha}$, (MAGE) mean amplitude of glucose excursion, (PPG) postprandial glucose, (ROS) reactive oxygen species, (SD) standard deviation

Keywords: continuous glucose monitoring system, diabetic complications, glycemic variability, indices of variability

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Introduction

The overall assessment of glycemic control in patients with diabetes should normally include the monitoring of three parameters, which are usually depicted as the "glucose triad": hemoglobin A1c (HbA1c), fasting plasma glucose (FPG), and postprandial glucose (PPG) excursions.

As for HbA1c, the two most relevant studies, the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications[1] and the United Kingdom Prospective Diabetes Study,[2] show that tight glucose control, with an improvement of HbA1c, can reduce diabetic complications in type 1 and type 2 diabetes, respectively. These studies are the basis for the American Diabetes Association's current recommended treatment goal that the HbA1c value be less than 7%.

As regarding fasting plasma glucose, it has been shown that its variability predicts the survival of type 2 diabetic patients,[3] increases the risk for incident cardiovascular disease events,[4,5] and might be an important risk factor for microvascular complications (retinopathy).[6]

The influence of PPG on diabetes complications has been examined intensively: the Hoorn study,[7] the Honolulu Heart Study,[8] the Chicago Heart Study,[9] and the Diabetes Epidemiological Collaborative Analysis of Diagnostic Criteria in Europe study[10] have clearly shown that the glucose serum level 2 hours after an oral challenge with glucose is a powerful predictor of cardiovascular risk; this evidence has also been confirmed by a meta-analysis of Coutinho and colleagues[11] and by interventional studies.[12,13]

However, one additional marker, the so-called "glucose variability," may be as important as the other three. The role of glycemic variability as an independent risk factor for diabetic complications was supposed by the authors of the DCCT study,[14] who evidenced that even when HbA1c values were comparable between intensively treated subjects and their conventionally treated counterparts, the latter group experienced a markedly higher risk of progression to retinopathy over time.

A speculative explanation is that glycemic excursions were of greater frequency and magnitude among conventionally treated patients (who received fewer insulin injections), generating more reactive oxygen species (ROS) in complication-prone cells because hyperglycemia-induced oxidative stress, resulting from the overproduction of ROS by the mitochondrial electron-transport chain, is the chief underlying mechanism of glucose-mediated vascular damage.[15]

More recently, many *in vitro*[16–20] and *in vivo*[21,22] studies have shown the importance of ROS as the main mechanism of glycemic variability-induced vascular complications.

At the moment, several glycemic variability indexes are used.[23–27] One of these, the mean of daily differences index, was used to assess interday glycemic variation; the others can be used to evaluate glycemic variability in a fixed interval of time (Δt).

The mean amplitude of glucose excursion (MAGE) index has been proposed by Service and associates[27] to quantify major swings of glycemia and to exclude minor ones. This was done by including for calculation only swings whose size was >1 standard deviation (SD) of the mean glycemic values obtained during the study period. Selection of the 1 SD criterion was based on the observation that only meal-related glucose swings in nondiabetic subjects were >1 SD. This index has been used by Monnier and colleagues[21] to evaluate glycemic variability from CGMS data; its correlation with urinary 8-iso-prostaglandin $F_{2\alpha}$ (iso-$PGF_{2\alpha}$) might indirectly provide "a validation" of the index; however, as the MAGE depends on the frequency of glucose measurements and the direction, either peak to nadir or nadir to peak, of the glucose excursions, it is open to several interpretations: in fact, in continuous monitoring the distinction between peaks and nadirs is unclear compared with the original hourly measurements used when the MAGE was devised. Thus, MAGE analysis ignores a large percentage of CGMS data.

Furthermore, we strongly believe that, in addition to the degree of excursion, the time in which it occurs (velocity of excursions) is important.

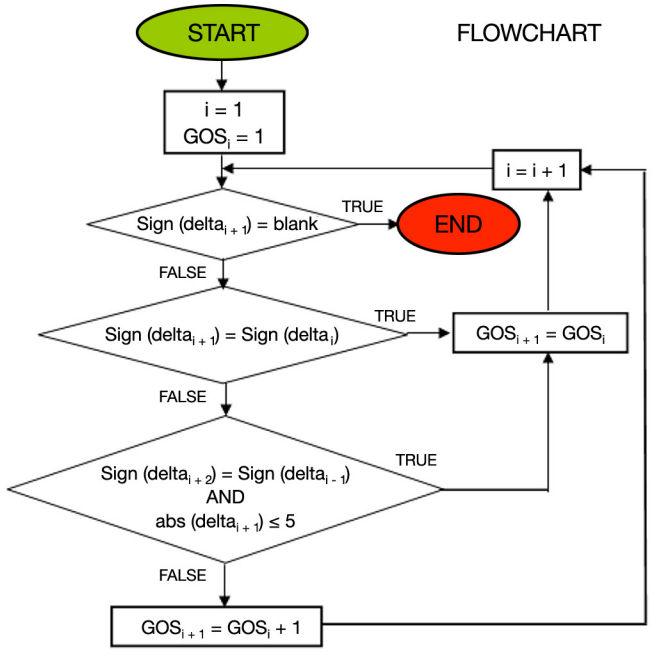
In order to avoid these limits, this article proposed a methodology supported by the need to find a nonarbitrary, flexible, and more standardized approach than the MAGE to define fluctuations in continuous glucose monitoring, and new indexes, to evaluate the velocity of glycemic excursions. Then, as validation of the method, we compared it with the MAGE calculated by a physician in the standard way.

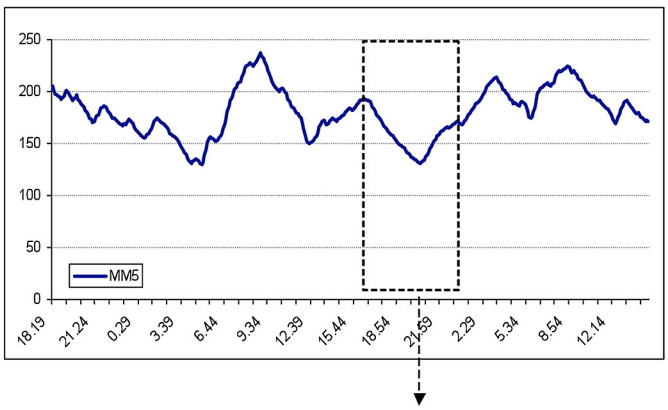
Methods

The group of signs (GOS) method is based on an algorithm; its main purpose is to divide systematically the continuous glucose monitoring line of a fixed interval of time (Δt) in subperiods or GOS for each subject with diabetes at any time. The method provides a number of GOS for each patient: each GOS could be positive when the glycemia increases or negative when the glycemia decreases.

The algorithm was tested on data collected from a continuous glucose monitoring system (CGMS® System Gold™, Medtronic) every 5 minutes for 3 days on 50 type 2 diabetic Caucasian subjects (age 62.3 ± 7.2, duration of disease 11.5 ± 9.6 years, no one in insulin therapy). It consisted of the following five steps.

1. Calculate the moving average with five terms (MM5) from CGMS glucose levels (sensor value), which allows small fluctuations to be smoothed and eliminated.
2. Calculate the difference between the two following MM5 terms (delta). The delta could be positive or negative when glucose increases or decreases, respectively. All null deltas will be removed from analysis.
3. Calculate the absolute value of delta (abs).
4. Calculate the delta sign (sign). The sign has two values: +1 if delta is positive and –1 if delta is negative.
5. Calculate GOS, which are groups of positive or negative deltas in glycemic monitoring. The GOS is a counter from 1 to n and starts with 1 and increases at each change of sign (**Figure 1**).





Time	MM5	Delta	abs_delta	Sign_Delta	GOS
16.29	194	-1	1	-1	29
16.39	193	-1	1	-1	29
16.54	192	-1	1	-1	29
16.59	191	-1	1	-1	29
17.04	190	-2	2	-1	29
17.09	188	-3	3	-1	29
17.14	185	-2	2	-1	29
17.19	183	-2	2	-1	29
...	...	...	...	...	...
20.04	134	-1	1	-1	29
20.09	133	-1	1	-1	29
20.14	132	-1	1	-1	29
20.39	131	1	1	1	30
20.54	132	1	1	1	30
20.59	133	1	1	1	30
21.04	134	3	3	1	30
21.09	137	2	2	1	30
21.14	139	3	3	1	30
...	...	...	...	...	...
22.44	164	1	1	1	30
22.54	165	1	1	1	30
23.09	166	-1	1	-1	30
23.34	165	1	1	1	30
23.44	166	1	1	1	30
23.49	167	1	1	1	30
23.59	168	1	1	1	30
0.14	169	1	1	1	30
0.29	170	1	1	1	30

A

B

N.B. The time gaps mean constant glucose example: at 16:29 to 16:39.

A GOS 29 has an amplitude of 63 mg/dl (sum of deltas), the excursion is negative (sign = –1), from 194 to 132 mg/dl, in about 195 minutes from 16:29 to 20:14 p.m.

B GOS 30 has an amplitude of 42 mg/dl (sum of deltas), the excursion is positive (sign = 1), from 131 to 170 mg/dl, in about 130 minutes from 20:39 to 00:29 p.m.

Figure 1. An example of GOS algorithm's application.

On the previous subject we applied the algorithm and obtained a decomposition of the 24-hour CGMS line in 41 GOS. Each GOS provides several pieces of information about that excursion. For example, GOS 29 has an amplitude of 63 mg/dl (sum of deltas), the excursion is negative (sign = –1), from 194 to 132 mg/dl, in about 195 minutes, from 16:29 to 20:14 p.m.

We used this algorithm to calculate, for each subject, the MAGE and other indices:

- MAGE_gos: mean of blood glucose (BG) increases or decreases (positive/negative GOS) from nadirs to peaks or vice versa when the GOS exceeds the value of 1 SD of the BG for the same 24-hour period.
- MAGE_abs_gos: mean of absolute value of GOS when the GOS exceeds the value of 1 SD of the BG for the same 24-hour period.
- Mean_gosN: mean of GOS greater than N mg/dl of BD.
- Stdev_gos: standard deviation of GOS.

Data were collected from a CGMS on 50 patients; for 8 patients we calculated all previous indexes and compared them with the MAGE calculated by a physician for each subject looking at a 24-hour CGMS graph (MAGE_phy) as in the standard way.

The protocol was approved by the local medical research ethics committee.

Results

Table 1 shows the high correlation coefficients, as evaluated by the Pearson test, between MAGE_phy and MAGEs calculated with the new procedure. All correlation coefficients are statistically significant with a p value <0.001 or p value <0.01 (**Table 1**).

Table 1.
High Correlation Coefficients between MAGE_phy and MAGEs Calculated with New Procedure

Pearson correlation[a]	MAGE_phy	MAGE_ gos	MAGE_ abs_gos	Mean_ gos50
MAGE_gos	98%*	—	—	—
MAGE_abs_gos	96%*	97%*	—	—
Mean_gos50	88%**	91%**	97%*	—
Stdev_gos	86%**	85%**	94%*	95%*

[a] Pearson correlations between GOS parameters and MAGE ones.
* p value <0.001, **p value <0.01.

Discussion

The MAGE is a tool used to investigate glycemic variability, but it does show some relevant limits. (1) The definition of glycemic peaks and nadirs is arbitrary or subjective; this is the main factor limiting its use in ambulatory, noncontrolled CGMS analyses. The MAGE uses the pooled results of arbitrarily designated glycemic peaks (chosen by the investigators in a nonreproducible fashion) and ignores blood glucose swings, which are designated as insignificant by the person interpreting data. (2) Selection of the direction according to the first glycemic excursion could undervalue the real amount of glycemic variability. (3) The utilization of 1 SD as the main criterion to express glycemic variability is another arbitrary rule of the MAGE. The choice of 1 SD derived from the observation that only meal-related glucose swings in nondiabetic subjects were >1 SD, but, now, it is well established that glycemic excursions in diabetic subjects cannot be comparable to glycemic variations observed in healthy controls because they are often unpredictable and strictly dependent on the kind of therapy prescribed.

Therefore, we designed and tested a new algorithm to calculate glycemic variability for 1 or more days or specific periods on the basis of 288 daily glycemic data. Preliminary data suggest that the proposed algorithm is a valid, efficient, and reliable method that may be used to calculate the standard MAGE on CGMS data and might be an alternative to MAGE: in fact, the MAGE_gos index allows avoiding the limit of the peaks' and nadirs' arbitrary choice (limit 1); MAGE_abs_gos, in addition, the limit of selection of the direction according to the first glycemic excursion (limit 2); and Mean_gosN, the utilization of one standard deviation (limit 3).

Furthermore, the algorithm also provides a basis to create other glycemic variability indices, such as the following:

> Exc_fast_max/stdev/mean/range: max, SD, mean, and range (max-min) of the ratio between the absolute value of GOS and the number of samples in the same GOS, which represents the BG increase/decrease every 5 minutes (velocity of excursions).

Conclusions

Diabetes is characterized by the development of specific micro- and macrovascular complications; a large number of studies have investigated and compared the roles of the

many factors involved in diabetic vascular alterations, but an accurate assessment of their respective contributions is still difficult. To date, the global assessment of glycemic control in diabetic subjects includes the "glucose triad": HbA1c, FPG, and PPG excursions.

However, many studies have shown the importance of a fourth variable, the glucose variability, as a risk factor for vascular dysfunctions; in addition, we believe that not only the degree of glucose swings but also the velocity of the oscillations could be involved in the genesis of diabetic complications. This is why we propose a new method (GOS) that allows evaluating both glycemic variability (more objectively) and the velocity of glucose swings; future studies, in which the indexes of velocity are compared with clinical surrogates (such as flow-mediated dilation and/or 8-iso-$PGF_{2\alpha}$), could confirm our hypothesis.

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