Diabetes & Metabolism xxx (2018) xxx–xxx

Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com

Review

The application of simple metrics in the assessment of glycaemic variability

L. Monnier [a,*], C. Colette [a], D.R. Owens [b]

[a] Institute of Clinical Research, University of Montpellier, 641, avenue du Doyen-Giraud, 34093 Montpellier cedex 5, France
[b] Diabetes Research Group, Institute of Life Science, Swansea University, Wales, UK

ARTICLE INFO

Article history:
Received 21 February 2018
Accepted 28 February 2018
Available online xxx

Keywords:
Assessment
Glycaemic variability
Impact

ABSTRACT

The assessment of glycaemic variability (GV) remains a subject of debate with many indices proposed to represent either short- (acute glucose fluctuations) or long-term GV (variations of HbA1c). For the assessment of short-term within-day GV, the coefficient of variation for glucose (%CV) defined as the standard deviation adjusted on the 24-h mean glucose concentration is easy to perform and with a threshold of 36%, recently adopted by the international consensus on use of continuous glucose monitoring, separating stable from labile glycaemic states. More complex metrics such as the Low Blood Glucose Index (LBGI) or High Blood Glucose Index (HBGI) allow the risk of hypo or hyperglycaemic episodes, respectively to be assessed although in clinical practice its application is limited due to the need for more complex computation. This also applies to other indices of short-term intraday GV including the mean amplitude of glycemic excursions (MAGE), Shlichtkrull's M-value and CONGA. GV is important clinically as exaggerated glucose fluctuations are associated with an enhanced risk of adverse cardiovascular outcomes due primarily to hypoglycaemia. In contrast, there is at present no compelling evidence that elevated short-term GV is an independent risk factor of microvascular complications of diabetes. Concerning long-term GV there are numerous studies supporting its association with an enhanced risk of cardiovascular events. However, this association raises the question as to whether the impact of long-term variability is not simply the consequence of repeated exposure to short-term GV or ambient chronic hyperglycaemia. The renewed emphasis on glucose monitoring with the introduction of continuous glucose monitoring technologies can benefit from the introduction and application of simple metrics for describing GV along with supporting recommendations.

Adopting a "glucocentric" approach to diabetes management requires targeting the 3 main components of dysglycaemia, i.e. chronic or ambient hyperglycaemia, glycaemic variability (GV) and hypoglycaemia. Each of these features, depicted as the "glycaemic triumvirate" [1] contributes to different degrees to the development and progression of diabetic complications [2]. Long-term interventional trials comparing intensive and conventional therapeutic strategies have clearly demonstrated that excess chronic/"ambient" hyperglycaemia is a major risk factor for the development of microvascular complications and to a lesser extent, macrovascular diseases [3]. The recent availability of more reliable devices for continuous glucose monitoring (CGM) have renewed the opportunity to further determine the clinical implications of GV with respect to the risk of developing vascular complications, especially in people with diabetes but also in prediabetes (impaired glucose tolerance). From a pathophysiological point of view the damages of GV on the vasculature are probably mediated through several biochemical disorders such as the activation of oxidative stress [4–6] and impairment of the Akt signalling pathway [7] that regulates cell proliferation, migration and angiogenesis. In a clinical context, GV can be a pathological contributor to diabetic complications through either acute glucose fluctuations (peaks to nadirs) [8,9] or longer-term variations in glucose homeostasis assessed by using monthly or quarterly self-monitoring of blood glucose (SMBG) in the fasting and/or postprandial [10] or changes in quarterly HbA1c levels [11]. At present, we lack of any long-term prospective interventional trials providing compelling evidence for a beneficial effect of reducing in short-term GV on "hard outcomes" such as the incidence rates of fatal and non-fatal cardiovascular events [major adverse cardiovascular events (MACE)] with available studies being either observational or retrospective. Some observational studies [4,5] have described an association between acute glucose fluctuations

* Corresponding author.
E-mail address: louis.monnier@inserm.fr (L. Monnier).

https://doi.org/10.1016/j.diabet.2018.02.008
1262-3636/

and markers of the activation of oxidative stress, one of the key players in the genesis of diabetic vascular complications [6]. However, recent interventional trials such as the FLAT-SUGAR trial failed to demonstrate significant improvements in surrogate cardiometabolic indices after therapeutic interventions aimed at reducing short-term GV [12]. The recent DEVOTE trial indicted [13,14] that individuals with a high day-to-day fasting GV had an increasing risk of severe hypoglycaemia (DEVOTE 2 [13]) predisposing them to two-fold increase risk of all-cause mortality and cardiovascular deaths in contrast to those who never suffered from severe hypoglycaemia (DEVOTE 3 [14]). These observations are in line with the fact that the risk for hypoglycaemia is related to the magnitude of acute glucose fluctuations [9]. The question then arises as to whether excess GV is an independent risk factor, facilitating and/or mediating the increased risk of cardiovascular events. Presently, the respective contributions of the 3 components of the "glycaemic triumvirate" to diabetic complications remain unclear. The objective of this present review is to clarify and provide further insight into this conundrum with particular references to the role of GV and cardiovascular complications of diabetes as compared to chronic glucose exposure and hypoglycaemia, where evidence-based recommendations are available [HbA1c $< 7\%$ to be modulated with the patient's vulnerability and hypoglycaemia defined as blood glucose (BG) < 70 mg/dL] [15]. However, the first recommendation for the short-term GV has been recently adopted by the consensus on use of continuous glucose monitoring [16] with a threshold set at 36% to differentiate between stable and unstable glycaemic control [9]. Advances in our knowledge about GV appear relatively slow although it should be borne in mind that more than 30 years have elapsed between the introduction of HbA1c as marker of chronic glucose exposure in the seventies [17] and its final well-recognized standardization by the International Federation of Clinical Chemistry and Medicine in 2002 [18].

Messages and thoughts on the metrics used to quantify GV: a contra-productive profusion?

GV is simply defined as the fluctuation of measurements of either glucose or other related parameters of glucose homeostasis (e.g. HbA1c) over a given interval of time [19]. In the 1970s, Service et al. introduced the mean amplitude of glycemic excursions (MAGE) considered to be the "gold standard" for assessing the short-term within-day GV [20]. Since then an ever-increasing number of new metrics of varying complexities have appeared in an attempt to better represent either short-term (within-day and between-day variability) or longer-term variability (Table 1) [21–24]. Such profusion of metrics of GV contributes to confusion based on differences between modalities of computation, advantages, limitations and means for interpretation (Table 1). Some of these indices required relatively complex mathematical computations and are not easily accessible and decipherable by health care professionals in routine clinical practice. Therefore, it is necessary to define measures of GV that can be easily computed, comprehended, and interpreted. There are predominantly two types of GV according to whether it is over a long or short time-interval. When the duration between two consecutive measurements is several weeks or months such as HbA1c measured quarterly, or serial fasting plasma glucose (FPG) and postprandial glucose (PPG) testing at the same frequency the variability is referred to as long-term or visit-to-visit variability [11]. Short-term GV is characterized by sudden and rapid upward or downward glucose changes usually within- or between-days based on either discontinuous or continuous monitoring of 24-h glycaemic profiles. Self-monitoring of blood glucose (SMBG) has been the main method for this purpose during the last 40 years [25,26], although in the past few years it is being replaced by continuous glucose monitoring (CGM) [16,27,28]. The main advantage of the CGM, which measures interstitial glucose is

Table 1
List of main metrics developed for assessing GV. For each index, short notes on computation, interpretation, advantages and limitations are indicated.

Metrics	Computation	Interpretation	Advantages/limitations
SD of glucose	From the mean square deviation (variance)	Short-term within-day glucose variability	Traditional measure of dispersion for large number of data such as those recorded with CGM systems and directly calculated by all devices
%CV for glucose	Calculated as %: [SD/mean glucose] $\times$ 100	Short-term within-day glucose variability. A value of 36% separates stable from unstable diabetes [6,26]	Adjusted on the mean glucose and easily computed from SD and mean by using a desktop calculator
MAGE	Mean differences from peaks to nadirs	Short-term within-day glucose variability	Major glucose fluctuations. Not directly given by the devices but requires a very simple calculation
MODD	24-hmean absolute differences between 2 values measured at the same time point	Short-term between-day glucose variability	Not directly given by the devices. Requires an additional computation, but easy to interpret
CONGA	Integrates the duration and degree of glucose excursions	Short-term within-day temporal glucose variability	Complex calculation
ADRR	Sum of the daily peak risks for hypo- and hyperglycaemia	Composite of short-term within- and between-day temporal glucose variability	Complex calculation
LBGI; HBGI	Preceded by a log transform to render symmetric the skewed distribution of glucose values	Risk indices for predicting hypo- or hyperglycaemia, respectively	Complex calculation. Both indices are more oriented toward investigating glucose tendency than variability
MAG	Incremental/decremental changes in glucose	Short-term within-day temporal variability	Relatively complex calculation
IQR of AGP	Distribution of glucose date at a given time point by using non-parametric statistics	Reflects the presence/absence of day-to-day synchrony in glucose patterns at a given time	Measure of dispersion for small number of data such as those recorded at a given time point over several days. Directly given by the Free Style Libre
Visit-to-visit changes	Measures of variability (SD, CV…) of HbA_{1c}, FPG… between sequential visits	Long-term variability in glucose homeostasis	Measures that are very heterogeneous in design

SD: standard deviation; %CV: coefficient of variation for glucose expressed as percentage; MAGE: mean amplitude of glycaemic excursions; CONGA: continuous overlapping net glycaemic acting; ADRR: average daily risk range; LBGI: Low Blood Glucose Index; HBGI: High Blood Glucose Index; MAG: mean absolute glucose variation; IQR: interquartile range (dispersion of data between the 25th and 75th percentile around the median); AGP: averaged glycaemic profile over several consecutive days (14 days with the Free Style libre®).

Please cite this article in press as: Monnier L, et al. The application of simple metrics in the assessment of glycaemic variability. Diabetes Metab (2018), https://doi.org/10.1016/j.diabet.2018.02.008