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Editorial

Glucose variability: Do we have to revisit the profusion of definitions to avoid confusion?

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In this issue of *Diabetes and Metabolism*, Lee et al. [1] report the results of the impact of visit-to-visit variability in fasting plasma glucose (FPG) on the all-cause mortality of persons with type 2 diabetes. This retrospective analysis was a 2-year follow-up of 3569 persons attending a medical centre in Taiwan. The population was divided into groups according to whether visit-to-visit variations in FPG were low, labile (decreasing, fluctuating and increasing) or high. The authors conclude, that in persons with diabetes, the visit-to-visit variability of FPG referred to as 'long-term' glucose variability should be maintained as low as possible.

These results are in broad agreement with previous publications on the long-term deleterious impact of glucose variability. The retrospective studies of Muggeo et al. [2], Kilpatrick et al. [3] and others [4–7], complemented by a meta-analysis [8] have indicated that both in type 1 and type 2 diabetes, high FPG and HbA_{1c} variability were associated with a greater risk for adverse clinical outcomes including either micro- or macro-vascular complications. However, the authors of the meta-analysis [8] noted that most studies suffered from inconsistencies in the definition of HbA_{1c} variability considered as 'long-term' glycaemic variability. Also, the impact of 'short-term' glycaemic variability, mainly within-day variability, on the development and progression of cardiovascular disease has never been established [9]. In an issue of Diabetes Care published in 2015, Hirsch [10] and Bergenstal [11] had a point-counterpoint debate. Hirsch argued that acute glucose fluctuations (within-day variability) are deleterious and should be a primary target [10]. Bergenstal however, argued that preferential consideration should be given to other markers than glycaemic variability [11]. The prospective FLAT-SUGAR trial [12] and the latest retrospective analysis of the clinical outcomes of the Diabetes Control and Complications Trial (DCCT) [9] failed to demonstrate any beneficial impact or influence of the 'short-term' (within-day glycaemic) variability on surrogate markers of cardiovascular disease [12] or on hard outcomes such as the risk for developing diabetic complications [9]. However, there arises the question as to whether the methodology used in both these analyses was appropriate. In the FLAT-SUGAR Study [12], reductions in the short-term glucose variability seen in the exenatide arm were not associated with changes in cardio-metabolic risk markers, due possibly to the use of insulin in both interventional arms capable of exerting an inhibitory effect upon the biological markers of inflammation and activation of the oxidative stress [13]. In the retrospective analysis of the DCCT database, the short-term variability relied on quarterly 7-point discontinuous glucose profiles [9], although advocated in clinical studies evaluating therapeutic agents [14] it lacks the precision of continuous glucose monitoring (CGM) conducted over prolonged periods of time [15–20]. Therefore, it remains questionable whether self-monitoring of blood glucose on a single day at quarterly time-intervals can be expected to represent chronic glycaemic exposure (sustained hyperglycaemia) and its relationship to long-term diabetic complications. Presently, despite progress in CGM technology, we are still lacking affordable wearable devices, with no constraints, over prolonged periods of time such as several months or years. Consequently, it remains difficult to prove the existence of a clear relationship between either or both acute and long-term glycaemic variations and diabetes related complications.

In the meantime, many inconsistencies exist in the definition of glycaemic variability along with a profusion of surrogate markers which make it difficult to gain a clear insight into the potential causative role, in any, of acute exaggerated glycaemic fluctuations as risk factors of adverse clinical outcomes. However, in animal studies such 'dangerous waves' [21] have an adverse effect on vascular endothelial cells, due to the activation and perpetuation of oxidative stress, acknowledged as one of the key players in the development and progression of diabetic complications [22,23]. Currently some of the markers of glycaemic variability are devoted to the assessment of short-term glucose variability, standard deviation around the 24-h mean glucose value (SD) and coefficient of variation for glucose (CV) [24–26] while others are used for assessing the long-term variability i.e. HbA_{1c} [8,27]. However, other metrics used for assessing short-term glucose variability, are presently too complex for use by healthcare professionals and to be integrated into routine care. Included among these are:

- the M-index described by Schlichtkrull in 1965 [28];
- the Mean Amplitude Glycemic Excursions (MAGE) and the Mean of Daily Differences (MODD) that were developed in the early

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1970s by Service and Molnar for assessing the within- and between-day glucose variability, respectively [29];
- others such as the Mean Absolute Glucose (MAG) change per hour, Continuous Overlapping Net Glycemic Action (CONGA), Average Daily Risk Rank (ADRR) and the Low and High Blood Glucose Index (LBGI or HBGI) [24–26].

The LBGI and HBGI, are oriented towards the risk prediction of adverse events such as hypoglycaemia or abnormal acute glucose peaks more than towards the specific assessment of glycaemic variability.

Characterising glycaemic variability includes either the measurement of glucose fluctuations or other parameters of glucose homeostasis over a given time-interval. This definition therefore covers two distinct types of measurements:

- firstly, the within-and between-day glucose variability determined over short periods of time;
- secondly, the visit-to-visit variability based on serial determinations of either FPG or HbA_{1c} at regular monthly or quarterly time-intervals.

The traditional measure of dispersion and variability for normal distributed data uses the standard deviation (SD) and the coefficient of variation (CV) defined as ([SD/[mean value]) $\times$ 100% in order to express the CV as a percentage. The daily within-day glucose variability, one of the most popular metrics of glycaemic variability, is referred to as the SD of glucose. However, the question remains whether the SD from a single day is a reliable reflection of the glycaemic variability. Consequently, physicians should be encouraged to calculate the within-day variability, over an extended period of time such as over several consecutive days and then average the daily SDs, called the "mean of within-day daily glucose variability" [24,25]. The relevance of this assessment should improve with increasing the duration of the monitoring period. However, if this period be extended beyond several days, especially when now using the new CGM devices, the within-day glucose variability needs to be referred to as 'intermediate', whilst also defining the time-period involved, rather than as 'short-term' variability. Another method that can be used to estimate the daily glucose variability is to calculate the SD of averaged daily blood glucose profiles. Such a marker referred to as the "daily SD by average" provides an SD, which is usually smaller than the "mean of daily SD" [30], with the underestimation becoming more and more marked as soon as the synchrony of glucose patterns from day-to-day becomes more and more altered [24]. A large disparity between the mean of daily SD for glucose and the daily SD by average reflects a high between-day glucose variability.

An additional parameter of glucose variability can be computed by calculating the dispersion of the glucose data at a given time-point over several consecutive days. This type of computation, which is provided by the Flash monitoring system of the Free style Libre, using the averaged glycaemic profile (AGP) over 14 days, reports the findings as IQRs (Interquartile Ranges). Large time point-to-time point variations in the IQRs indicates a loss of synchrony of glucose patterns from day-to-day, i.e. a high between-day variability (Fig. 1) in contrast to small IQR when between-day glucose variation is relatively small [24] (Fig. 1).

Although we have focused on SD and CV as the metrics of glucose variability and deliberately omitted the others that require mathematical skills, interpretation can still be somewhat difficult. Therefore, simplifying the findings appears a prerequisite in order that any healthcare provider can easily assess and interpret the degree of short-term glycaemic variability. According to our most recent research in this field, the CV for glucose seems to be the most appropriate index for assessing the mean daily within-day variability. As the SD for glucose is usually positively correlated with the mean glucose value, the CV renders the assessment of glycaemic variability independent of the mean glucose concentration, i.e. on one of the parameters that reflects the chronic glycaemic exposure. We have demonstrated that it can be a useful and simple tool for separating stable from labile diabetes by setting the cut-off value for the CV at 36% [31]. Previously, Hirsch had proposed as an ideal target for glycaemic variability an SD calculated from the following formula SD $\times$ 3 mean glucose, i.e. a CV $<$ 33%, a value similar to that observed in our study [32].

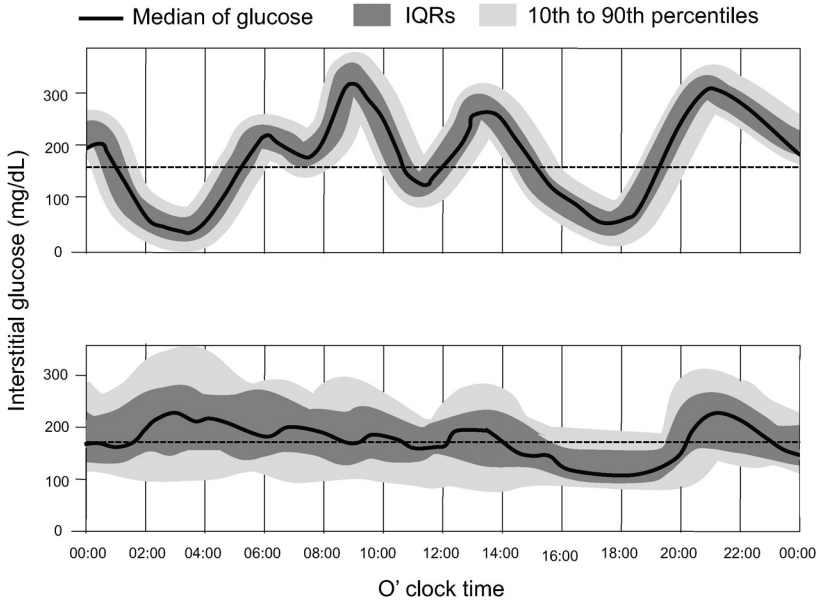

Fig. 1. Averaged glucose profiles (AGPs) from two patients with the same averaged median interstitial glucose value (165 mg, black dotted line). The displayed glucose profiles and medians of glucose (black solid lines) are 14 days of CGM data. Shaded dark areas correspond to either IQRs (Interquartile ranges) or 10–90th percentiles. The upper panel is the illustration of a patient in whom the synchrony of glucose patterns is relatively preserved, i.e. with a small between-day glucose variability characterized by small IQRs and small time point-to-point IQR variations. The bottom panel is the illustration of a patient with a high loss of synchrony from day-to-day in glucose patterns, i.e. a high between-day glucose variability (high time-to-time IQR variation).

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