Glucose Variability; Does It Matter?

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Overall lowering of glucose is of pivotal importance in the treatment of diabetes, with proven beneficial effects on microvascular and macrovascular outcomes. Still, patients with similar glycosylated hemoglobin levels and mean glucose values can have markedly different daily glucose excursions. The role of this glucose variability in pathophysiological pathways is the subject of debate. It is strongly related to oxidative stress in *in vitro*, animal, and human studies in an experimental setting. However, in real-life human studies including type 1 and type 2 diabetes patients, there is neither a reproducible relation with oxidative stress nor a correlation between short-term glucose variability and retinopathy, nephropathy, or neuropathy. On the other hand, there is some evidence that long-term glycemic variability might be related to microvascular complications in type 1 and type 2 diabetes. Regarding mortality, a convincing relationship with short-term glucose variability has only been demonstrated in nondiabetic, critically ill patients. Also, glucose variability may have a role in the prediction of severe hypoglycemia. In this review, we first provide an overview of the various methods to measure glucose variability. Second, we review current literature regarding glucose variability and its relation to oxidative stress, long-term diabetic complications, and hypoglycemia. Finally, we make recommendations on whether and how to target glucose variability, concluding that at present we lack both the compelling evidence and the means to target glucose variability separately from all efforts to lower mean glucose while avoiding hypoglycemia. **(*Endocrine Reviews* 31: 171–182, 2010)**

I. Introduction

Patients with similar mean glucose or glycosylated hemoglobin (HbA1c) values can have markedly different daily glucose profiles, with differences both in number and duration of glucose excursions. Hyperglycemia is thought to induce oxidative stress and interfere with normal endothelial function by overproduction of reactive oxygen species, which results in diabetic complications through several molecular mechanisms (1, 2) (Fig. 1). In addition, glucose variability might contribute to these processes as well. Since the publication of the results of the Diabetes Control and Complications Trial (DCCT) in the early 1990s (3, 4), the topic of glucose variability as a contributor to diabetic complications has been debated. It was suggested that glucose variability might explain the difference in microvascular outcome between the intensively and conventionally treated type 1 diabetes patients with the same mean HbA1c throughout the trial (5). Although this hypothesis was refuted recently by the statisticians of the DCCT/Epidemiology of Diabetes Interventions and Complications (EDIC) themselves (6), subsequent hypotheses on the relation of glucose variability to oxidative stress in type 2 diabetes patients and to mortality in patients with stress hyperglycemia have been postulated.

Glucose variability and lack of predictability are issues that diabetes patients and doctors encounter in daily practice. In this review article, we will first provide an overview of the various methods to measure glucose variability. Second, we review the current evidence for the relation between glucose variability and oxidative stress, long-term

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Abbreviations: 1,5-AG, 1,5-Anhydroglucitol; CF, cortical fibroblast(s); CGM, continuous glucose measurement; CONGA, continuous overlapping net glycemic action; CV, coefficient of variation; HbA1c, glycosylated hemoglobin; ICU, intensive care unit; MAGE, mean amplitude of glycemic excursions; MODD, mean of daily differences; $PGF_{2\alpha}$, prostaglandin $F_{2\alpha}$; PICU, pediatric ICU; PTC, proximal tubule cell(s); SMBG, self-monitored blood glucose.

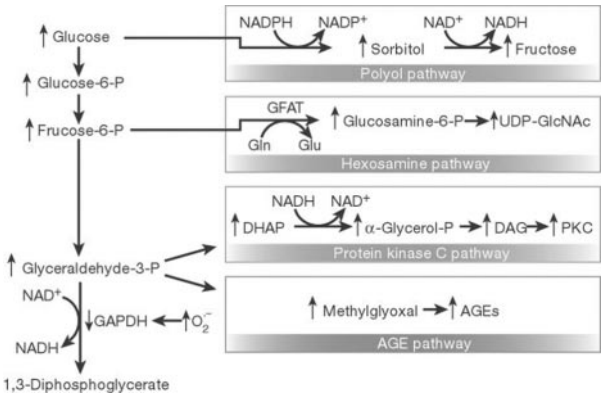

Fig. 1. Potential mechanism by which hyperglycemia-induced mitochondrial superoxide overproduction activates four pathways of hyperglycemic damage. [Reproduced with permission from M. Brownlee: *Nature* 414:813–820, 2001 (1) © Macmillan Publishers, Ltd.]

diabetic complications, and severe hypoglycemia. Lastly, we will make recommendations for treatment with regard to targeting glucose variability. We performed a structured literature search using PubMed and Embase according to the PICO (patient, intervention, comparison, and outcome) method (7), including relevant literature published online up to March 2009.

Especially in type 2 diabetes, postprandial hyperglycemia contributes to individual glucose variability. However, because postprandial hyperglycemia is different from glucose variability as defined above, we will not discuss this further, other than to say that the positive relationship between postprandial hyperglycemia and cardiovascular risk supports the possibility that glucose variability may be related to cardiovascular risk as well (8).

II. Different Methods for Glucose Variability Measurement

There are several methods to quantify glucose variability, but there is no universally accepted "gold standard." Figure 2 describes the formulas underlying the different measures and their characteristics. Most authors consider glycemic variability as a standard of intraday variation, reflecting the swings of blood glucose in a diabetic patient as a consequence of diminished or absent autoregulation and the shortcomings of insulin therapy.

The easiest way to get an impression of the glucose variability in an individual patient is to calculate the SD of glucose measurements and/or the coefficient of variation (CV), if one wishes to correct for the mean. It is possible to calculate SD and CV from seven-point glucose curves, facilitating their use in daily practice. On the other hand, when obtaining seven-point glucose curves, certain peaks or nadirs will always be missed simply because they occur between two measurements, making this method less accurate. Calculating SD and CV from continuous glucose measurement (CGM) data seems preferable, but in daily practice it is impossible to obtain CGM data from each individual patient. Also, the extent to which CGM-assessed SD differs from that calculated from seven-point profiles has not, to our knowledge, been formally investigated.

In 1964, Schlichtkrull *et al.* (9) defined a new measure, the M-value, trying to quantify glycemic control of diabetes patients. It is a measure of the stability of the glucose excursions in comparison with an "ideal" glucose value of 6.6 mmol/liter (120 mg/dl), developed using six self-monitored blood glucose (SMBG) values per 24 h in 20 patients with type 1 diabetes. Later, other "ideal" glucose levels from 4.4 to 5.6 mmol/liter (80 to 100 mg/dl) were proposed to obtain the best formula (10). In the final formula, choice of the ideal glucose value is left up to the investigator, making it difficult to compare different studies that use different ideal glucose values. The M-value is zero in healthy controls, rising with increasing glycemic variability or poorer glycemic control, making it difficult to distinguish between patients with either high mean glucose or high glucose variability. Moreover, because hypoglycemia has a greater impact on the M-value than hyperglycemia, it is more a clinical than a mathematical indicator of glycemic control.

In 1970, Service *et al.* (11) described a method that is widely used nowadays: the mean amplitude of glycemic excursions (MAGE). Developed using hourly blood glucose sampling for 48 h, this method generates a value for the variation around a mean glucose value by summating the absolute rises or falls encountered in a day. The reference point here is the mean glucose value rather than an arbitrarily chosen ideal value. Arbitrarily, it ignores excursions of less than 1 SD. This may incorrectly disregard possibly important smaller excursions. MAGE was originally defined from hourly glucose sampling for 48 h in 14 patients. Thus, it has never been formally validated for calculation from seven-point glucose profiles; neither do we know how the MAGE calculated from CGM data corresponds to the originally developed value.

An intraday measurement of glycemic variability specifically developed for use on CGM data was proposed in 1999 by McDonnell *et al.* (12), *i.e.*, continuous overlapping net glycemic action (CONGA-*n*). It is calculated as the SD of the summated differences between a current observation and an observation *n* hours previously. Because CONGA does not require arbitrary glucose cutoffs or arbitrarily defined rises and falls, it seems to be a more objective manner to define glucose variability than M-value or MAGE. It is proposed for CONGA-*1*, CONGA-*2*, and

Variability measure	Formula	Explanation of symbols	Discriminating feature
SD	$\sqrt{\frac{\sum (x_i - \bar{x})^2}{k-1}}$	x_i = individual observation $\bar{x}$ = mean of observations k = number of observations	easy to determine, extensively used
CV	$\frac{s}{\bar{x}}$	s = standard deviation $\bar{x}$ = mean of observations	easy to determine, SD corrected for mean
adjusted M-value	$M_{GR} + M_W$ where $M_{GR} = \frac{\sum_{t=t_1}^{t_k} \left\lvert {}^{10}\log \frac{GR_t}{IGV} \right\rvert^3}{n}$ and $M_W = \frac{G_{max} - G_{min}}{20}$	M_{GR} = M-value for glucose readings M_W = correction factor for n <24 GR_t = glucose reading at time t IGV = ideal glucose value t_i = time in minutes after start of observations of the ith observation G_{max} = maximum glucose reading G_{min} = minimum glucose reading	not a pure variability measure
MAGE	$\sum \frac{\lambda}{n}$ if $\lambda \succ v$	λ = each blood glucose increase or decrease (nadir-peak or peak nadir) n = number of observations v = 1 SD of mean glucose for 24-hr period	used most extensively
CONGA	$\sqrt{\frac{\sum_{t=t_1}^{t_{k*}} (D_t - \bar{D})^2}{k^* - 1}}$ where $D_t = GR_t - GR_{t-m}$ and $\bar{D} = \frac{\sum_{t=t_1}^{t_{k*}} D_t}{k^*}$	k* = number of observations where there is an observation n x 60 minutes ago $m = n \times 60$ D_t = difference between glucose reading at time t and t minus n hours ago	specifically developed for CGM
MODD	$\frac{\sum_{t=t_1}^{t_{k*}} \lvert GR_1 - GR_{t-1440} \rvert}{k^*}$		inter-day variation

SD=standard deviation; CV=coefficient of variation; MAGE=mean amplitude of glycemic excursions; CONGA=continuous overall net glycemic action; MODD=mean of daily differences; SMBG=self monitored blood glucose; CGM=continuous glucose monitoring. Units are in mmol/l or mg/dl depending on the unity of the glucose values measured. To convert glucose values from mg/dl to mmol/l multiply by 0.0555.

Fig. 2. Formulas used in describing glucose variability.

CONGA-4, but it is not known which, if any, of these is preferable.

When examining glucose variability, the interday variation in blood glucose is also of interest. In 1972, Molnar *et al.* (13) observed different day to day glucose patterns in patients with a similar MAGE. They proposed the absolute mean of daily differences (MODD) as a supplement to the MAGE and mean blood glucose. The MODD is the mean absolute value of the differences between glucose values on 2 consecutive days at the same time. In daily practice, eating habits play an interfering role because different mealtimes will influence MODD. Developed using hourly blood sampling during 48 h, the validity of its use on seven-point glucose curve data or CGM is unknown.

The most straightforward and easy way to measure interday variability is calculating the SD of fasting blood glucose concentrations (14). However, it is more a measure of long-term glucose variability because it takes values of at least 2 consecutive days to calculate. Above all, fasting glucose variability neglects the variability in all other intraday glucose values.

Besides the commonly used measurements described above, several other methods have been proposed that have not gained widespread use: the blood glucose rate of change, computed for CGM, describing the magnitude of temporal fluctuations of blood glucose levels using logarithmically transformed glucose data (15–17); the mean absolute difference of consecutive glucose values, vali-

dated for SMBG curves (18); the "J"-index, defined as the square of the mean plus SD of glucose measurements, excluding severe and persistent hypoglycemia, which is validated for SMBG curves (19); and the lability index, based on the change in glucose levels over time (20). The complexity of the calculations (17) or substantial similarity with other measures (18, 19) probably underlie their limited use.

The MAGE is most commonly used for CGM data and SD/CV for SMBG curves. It has to be mentioned that blood glucose values are seldom normally distributed, a mathematical condition for use of the SD (16). In literature, this limitation is mostly ignored. However, for SMBG strong correlations between variability measures, expressed as SD and mean absolute difference, have been described (18). Using data from a previous study (21), we also identified strong and significant correlations between cited variability measures ($r = 0.63–0.93$; $P = 0.01$; our unpublished data), suggesting a high degree of overlap between the different measures when using CGM data. Because the SD correlates highly with all other variability measures, it seems of little concern that the SD does not take the number of glycemic swings into account (Fig. 3), whereas the calculation of MAGE, MODD, and CONGA is based on this. Whether calculating MAGE, MODD, CONGA, or other measures simultaneously helps to get additional insight in pathophysiological processes needs further investigation. A further complication is that the time needed to reliably assess a given standard of variability is not known. Preliminary results suggest that this may take several days of CGM measurements (22).

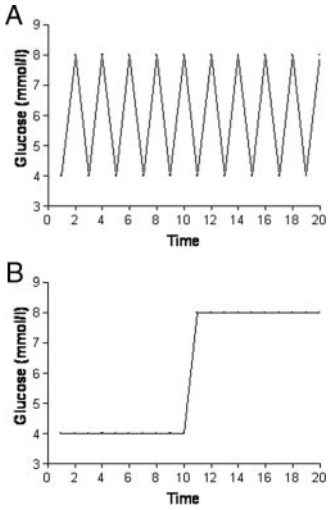

Fig. 3. Two fictitious patients with identical mean glucose and SD, but different patterns of variability. A and B are two different patients with different patterns of variability but the same mean glucose (6.0 mmol/liter) and SD (2.1). SD is calculated as the square root of the variance: $\sqrt{\frac{\Sigma(x_i - \bar{x})^2}{k-1}}$, where x_i is the sample of the i^{th} observation, $\bar{x}$ the mean of all the observations, and k is the number of observations.

In addition to methods to quantify glucose variability derived from direct glucose measurements, serum determination of 1,5-anhydroglucitol (1,5-AG) has been suggested as a measure of glycemic excursions (23). 1,5-AG is a polyol kept within stable limits in subjects with glucose values in the normal range. Its reabsorption in the kidney is inhibited by excessive excretion of urinary glucose; the higher the plasma glucose concentration, the lower the plasma 1,5-AG concentration (24). Urinary glucose appears at a plasma glucose concentration of approximately 8.8–10.5 mmol/liter (160–190 mg/dl), so despite a very quick response of this marker to changes in plasma glucose levels, it seems of little use detecting glucose fluctuations below this range. Also, the correlation between glucose variability and 1,5-AG is weak when HbA1c values are above 8% (25, 26). Measurement of 1,5-AG concentrations seems therefore only of use when looking at hyperglycemic excursions, *i.e.*, postprandial hyperglycemia in patients with an HbA1c below 8%.

In summary, we suggest SD as the preferable method when quantifying variability from CGM data because this is the easiest and best validated measure. Also, as further explained below, SD was the measure used in the only field so far where a relation between glucose variability and hard outcomes could be demonstrated, *i.e.*, mortality in intensive care unit (ICU) patients.

III. Contribution of Glucose Variability to Oxidative Stress

The current hypothesis about the link between hyperglycemia and diabetic complications suggests that the hyperglycemia-driven formation of reactive oxygen species enhances four mechanisms of tissue damage: the polyol pathway, the hexosamine pathway, protein kinase C activation, and formation of advanced glycation end-products (1) (Fig. 1). It should, however, be noted that at this time no human intervention studies have been published that establish a causal relation between oxidative stress and micro- or macrovascular complications (27). Moreover, daily antioxidant supplementation does not reduce the risk of cardiovascular events and microvascular complications (28). However strong the evidence supporting the concept of hyperglycemia-induced oxidative stress may be, the role of glycemic variability in the formation of oxidative stress is much more controversial. *In vitro*, animal and human studies in experimental settings consistently report a deleterious effect of intermittent high glucose, either larger than or as large as constant high glucose, despite less total glucose exposure, but these findings cannot be reproduced in real-life human studies.

Quagliaro *et al.* (29) and Piconi *et al.* (30) demonstrated that intermittent high glucose levels stimulate reactive oxygen species overproduction leading to increased cellular apoptosis in human umbilical vein endothelial cells compared with a stable high glucose environment. In these studies, three groups of cells were compared, each group receiving a different fresh medium every 24 h for 14 d: a continuously normal glucose medium (5 mmol/liter), a continuously high glucose medium (20 mmol/liter), and normal and high glucose media alternating every 24 h (5 and 20 mmol/liter, respectively).

The effect of glycemic variation *vs.* constant high glucose was also studied in cells of the kidney. Takeuchi *et al.* (31) examined the effects of periodic changes in extracellular glucose concentration on matrix production and proliferation of cultured rat mesangial cells. Mesangial cell matrix production, measured as collagen III and IV protein production and DNA level, was examined as a marker of cell proliferation and nephropathy development (32, 33). Three groups of cells were used, receiving a different glucose medium every 24 h (5 mmol/liter, alternating 5 and 25 mmol/liter, and 25 mmol/liter, respectively) for 10 d. They reported a significantly larger collagen III and IV protein and DNA production in the alternating glucose group compared with the continuous high glucose group. No mechanism for these effects was demonstrated.

Jones *et al.* (34) investigated the effects of constant and intermittently increased glucose on human kidney proximal tubule cells (PTC) and cortical fibroblasts (CF). In this study, cell growth was assessed by thymidine uptake as an index of DNA synthesis, collagen synthesis as a marker of extracellular matrix production, and protein content. They exposed three groups of cells for 4 d to 6.1 mmol/liter, 25 mmol/liter, or alternating 6.1 and 25 mmol/liter glucose with daily medium change. Overall, the alternating glucose cells showed larger thymidine uptake (PTC and CF) and more collagen synthesis (CF) than the cells exposed to a stable high glucose medium. Nevertheless, no differences between the high and intermittent glucose groups were found in cell protein content in both PTC and CF. On the cytokine level, alternating high glucose activated more TGF-β1 and IGF binding protein-3 than stable high glucose, suggesting more collagen synthesis, potential apoptosis, and biological activity of IGF-I, which has been implicated in the development of diabetic nephropathy (35, 36).

Horváth *et al.* (37) built on these findings and compared the effect of nontreated diabetes (continuous high glucose) with intermittently insulin-treated diabetes (oscillating glucose) on the development of endothelial dysfunction in 19 male Wistar rats. After 10 d of insulin treatment, they monitored blood glucose levels every 6 h for 48 h in total. After these 48 h the rats were killed, and organs were harvested. Their main finding was that the intermittently treated rats showed a significantly larger impairment in endothelial function compared with the nontreated animals despite lower total glucose exposure, with indications for an effect of the poly(ADP-ribose) polymerase pathway.

The human studies performed are less consistent in their findings. Ceriello *et al.* (38) performed a normoinsulinemic hyperglycemic glucose clamp study investigating the relation between glucose variability, oxidative stress [assessed as plasma 3-nitrotyrosine and 24-h excretion rates of free 8-iso-prostaglandin $F_{2\alpha}$ (8-iso-$PGF_{2\alpha}$)], and endothelial function, measured by flow-mediated dilatation. Type 2 diabetic patients as well as healthy controls were studied. They suggested that an oscillating glucose level has more deleterious effects on endothelial function and enhances oxidative stress more than a constant high glucose level. To mimic glucose variability, glycemia was increased from 5 to 15 mmol/liter and back every 6 h for 24 h. Stable hyperglycemia conditions at 10 and 15 mmol/liter for 24 h were the comparators.

It can be debated how many consecutive periods with alternating degrees of glycemia are necessary to reliably assess glycemic variability rather than the effect of repeated stimuli. From the field of pituitary function assessment, it is known that repeated stimuli can result either in extinction of the response or exaggerated response (39). Also, in everyday life, glucose swings of a patient with diabetes have a duration of less than 6 h and occur more frequently than the two 6-h cycles used in the study performed by Ceriello *et al.* (38). As already acknowledged in one of these manuscripts (31), the duration of alternating glycemia is also an important comment on the *in vitro* studies described earlier because they alternate their glucose media every 24 h.

Three studies investigated the correlation between glucose variability assessed using CGM and oxidative stress in a nonintervention design (Fig. 4). These studies calculated the MAGE to assess glucose variability and 24-h urinary excretion rates of 8-iso-$PGF_{2\alpha}$ to assess oxidative stress. The first study was performed by Monnier *et al.* (40) in 21 type 2 diabetes patients. They found a strong correlation between glucose variability and oxidative stress ($r = 0.86$; $P < 0.001$). The second study was performed by Wentholt *et al.* (21) in 25 type 1 diabetes patients. They expected to find an even stronger correlation because of the greater glucose variability in type 1 diabetes patients, but they could not confirm the findings of Monnier ($r = 0.28$; no P value reported). A possible explanation for this discrepancy is that the studies used a different method to quantify 8-iso-$PGF_{2\alpha}$ excretion rates. Tandem

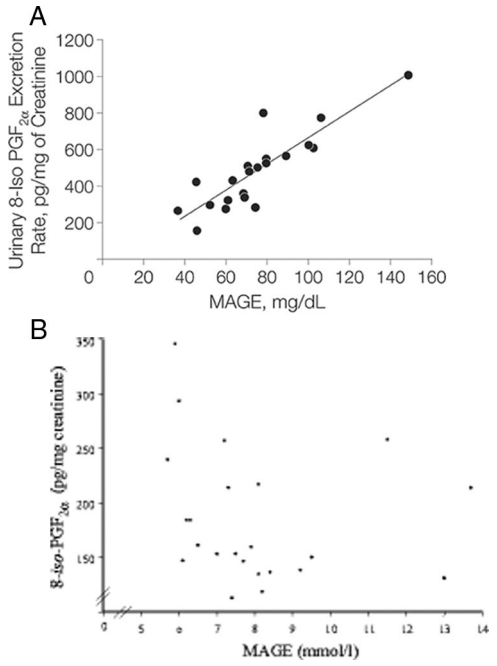

Fig. 4. Different relations between glucose variability and oxidative stress in type 2 and type 1 diabetes. Correlation between glucose variability, expressed as MAGE, and oxidative stress, expressed as urinary excretion rate of 8-iso-$PGF_{2\alpha}$, in type 2 (A) and type 1 (B) diabetes patients. A, $r = 0.86$; B, $r = 0.26$. [Panel A is reproduced with permission from L. Monnier, *et al.*: *JAMA* 295:1681–1687, 2006 (40) © American Medical Association. Panel B is reproduced from Fig. 3 with kind permission from I.M. Wentholt, *et al.*: *Diabetologia* 51:183–190, 2008 (21) © Springer Science + Business Media.]

mass spectrometry, used by Wentholt, is not hampered by cross-reactivity of structurally (un)related components of 8-iso-$PGF_{2\alpha}$, whereas the immunoassay used by Monnier is more susceptible to interference (40). To solve this contradiction, our group reexamined this relationship in 24 type 2 diabetes patients quantifying urinary 8-iso-$PGF_{2\alpha}$ excretion rates with tandem mass spectrometry (41). We could not reproduce a relationship between glucose variability and oxidative stress ($r = 0.12$; $P = 0.53$).

One intervention trial has been performed to assess the effect of lowering glucose variability on oxidative stress (42). This crossover trial compared the effect of a basal insulin regimen and a mealtime insulin regimen on glucose variability and oxidative stress in type 2 diabetes using CGMS data (n = 40). Although glucose variability tended to be lower (9%; P = nonsignificant) in the mealtime insulin group, no difference in oxidative stress was found. If anything, there was more oxidative stress in the mealtime insulin group. Again, no correlation between glucose variability and oxidative stress determined by 24-h urinary excretion rates of 8-iso-$PGF_{2\alpha}$ was seen in these insulin-treated type 2 patients. In this study, 8-iso-$PGF_{2\alpha}$ was quantified by tandem mass spectrometry.

Summarizing, *in vitro* studies do show a relationship between glycemic variability and oxidative stress-induced apoptosis and renal cell proliferation in cultured human or rat cells. These findings are confirmed in an animal study, but this relation could not be consistently reproduced in human studies. Differences in duration and frequency of the periods with alternating glycemia as well as differences in methods used for oxidative stress quantification are possible explanations for these discrepant findings.

IV. Contribution of Glucose Variability to Diabetic Complications and Poor Outcomes in Critically Ill Patients

The most important issue for clinical practice is whether glucose variability contributes to morbidity and mortality irrespective of the pathophysiological mechanism. This issue was studied retrospectively in type 1 diabetes patients (6, 43–47) and in critically ill patients at the adult (48–50) and pediatric (51, 52) ICU.

The DCCT, a randomized controlled trial which included 1441 patients with type 1 diabetes, presented statistical models in 1995 suggesting a connection between variability in blood glucose and the occurrence of microvascular complications (4). At similar HbA1c levels throughout the study, patients from the conventionally treated group were thought to be at higher risk for microvascular complications, particularly progression of retinopathy, than those in the intensively treated group. Kilpatrick *et al.* (43, 44) independently performed analyses of the data of the DCCT showing that the variability in blood glucose around a patient's mean value (SD) was not related to the development or progression of either retinopathy or nephropathy in type 1 diabetes patients. More than 10 yr later, the DCCT statisticians themselves corrected their previous findings and refuted the relation suggested earlier (6). As opposed to short-term glucose variability, long-term fluctuations in glycemia, expressed as HbA1c variability, may contribute to the development of retinopathy and nephropathy in the DCCT group (45).

Bragd *et al.* (46) performed a prospective observational study in 100 type 1 diabetes patients, collecting five-point self-monitoring glucose data for 4 wk. Data on the incidence and prevalence of micro- and macrovascular complications as well as peripheral neuropathy were obtained during an 11-yr follow-up. This study confirmed the findings of the studies mentioned previously in this section, finding no relationship between short-term glucose variability measured as SD and microvascular complications. However, they found that glucose variability was significantly related to the presence of peripheral neuropathy and was a borderline predictor of its incidence (hazard ratio, 1.73; $P = 0.07$), suggesting that the nervous system

may be vulnerable to glycemic variability. On the other hand, recent analysis of the more extensive DCCT datasets did not show any relation between glucose variability and the prevalence of diabetic peripheral as well as autonomic neuropathy (47).

A single study in type 2 diabetes patients examined the effect of glucose variability on retinopathy (53). The coefficient of variation of fasting plasma glucose was retrospectively calculated in 130 patients without retinopathy at baseline with an average follow-up of 5.2 yr. The frequency of glucose measurements ranged from quarterly to yearly, so long-term variability of fasting plasma glucose was assessed. The highest quartile of variation in fasting plasma glucose contributed to diabetic retinopathy independently from and in addition to HbA1c (odds ratio, 3.68; $P = 0.049$). This finding is in line with the above-noted relation of long-term fluctuations in glycemia to the development of retinopathy in type 1 diabetes (45).

Recently, a randomized controlled trial was published comparing the effects of a prandial and a basal insulin regimen with respect to cardiovascular outcomes in type 2 diabetes patients after acute myocardial infarction (HEART2D Trial, Ref. 54). The authors concluded that a significant difference in postprandial glucose values, while achieving comparable HbA1c values, was not associated with a difference in cardiovascular outcome. Glucose variability was not separately assessed, but visual evaluation of the mean glucose profiles collected during the study seems to show a difference in glucose variability in favor of the prandial insulin group that did not translate into improved outcome (Fig. 5).

Glucose variability has also been studied in critically ill patients. Three different groups performed retrospective analyses of glucose variability as a predictor of mortality at the adult ICU (48–50). All three groups concluded that glucose variability measured as SD was a significant predictor of mortality in critically ill patients independently from severity of illness. The finding that mortality significantly increased with variability in different strata of mean glucose level (50) contributes to the suggestion that variability is a predictor of mortality independent from mean glucose level (Fig. 6). Egi *et al.* (49) performed a subgroup analysis of patients with diabetes. Interestingly, in this group glucose control, as assessed by the SD and mean glucose, displayed no relation with survival in contrast to patients without diabetes. These results may suggest that patients with diabetes "get accustomed" to fluctuating glucose levels, making them less devastating.

Not only in the adult ICU, but also in two different pediatric ICUs (PICUs), the influence of glycemic variability was studied. Wintergerst *et al.* (52) retrospectively reviewed all PICU admissions of 1 yr, excluding patients

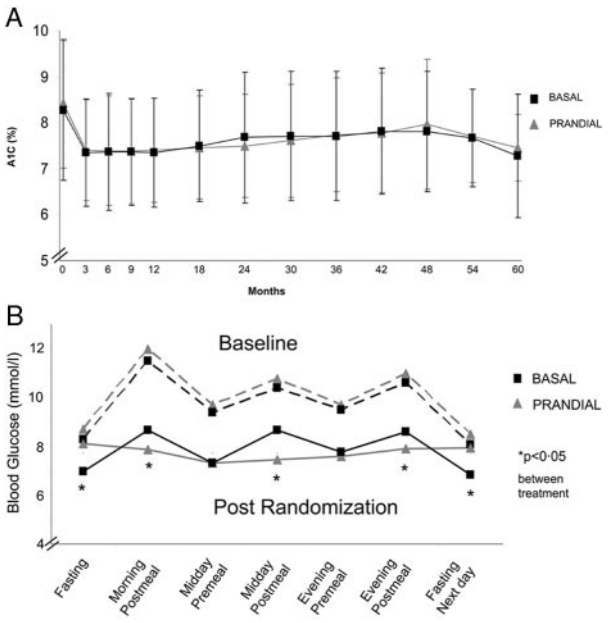

Fig. 5. Glycemic measures in a randomized controlled trial comparing a prandial with a basal insulin regimen. A, Mean (SD) HbA1c by treatment strategy. B, Seven-point mean SMBG profiles at baseline (*dotted line*) and throughout the study (*solid line*) by treatment strategy. [Reproduced from Fig. 2 with permission from I. Raz, *et al.*: *Diabetes Care* 32:381–386, 2009 (54) © American Diabetes Association in the format Journal via Copyright Clearance Center.]

with a known diagnosis of diabetes mellitus (n = 1094). Glucose variability was assessed as the mean of the absolute differences between sequential glucose values divided by the differences in collection time. The second retrospective cohort analysis was performed by Hirshberg *et al.* (51). They included all PICU admissions with a length of stay of more than 24 h in 1 yr, excluding patients above 18 yr of age, patients with known diabetes mellitus, or when insulin therapy was administered during PICU stay (n = 863). Glucose variability was described as a patient who suffered from both hyperglycemia (≥8.3 mmol/liter) and hypoglycemia (≤3.3 mmol/liter) during PICU stay, which occurred in 6.8% of all patients. Both of these studies

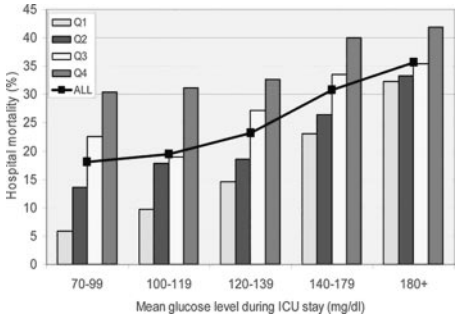

Fig. 6. Hospital mortality related to mean glucose and glycemic variability. Q1, Lowest quartile of glycemic variability; Q4, highest quartile of glycemic variability. To convert mean glucose from mg/dl to mmol/liter, multiply by 0.0555. [Reproduced from Fig. 1 with permission from J.S. Krinsley: *Crit Care Med* 36:3008–3013, 2008 (50) © Wolters Kluwer Health.]

confirmed the earlier described adult data showing that glucose variability is associated with mortality and increased length of stay in this population, and they even show a stronger association than hyperglycemia, although only the latter study was adjusted for severity of illness in multivariate analysis.

van den Berghe *et al.* (55) published a landmark trial in 2001 showing a dramatic 42% relative reduction in mortality in the surgical ICU when blood glucose was normalized to 4.4–6.1 mmol/liter compared with 9.9–11.0 mmol/liter. Recently, the purported benefits of tight glycemic control in the ICU have been challenged. The NICE-SUGAR study (56) showed that intensive glucose control (4.5–6.0 mmol/liter compared with <10 mmol/liter) increased mortality among adults in the ICU (odds ratio, 1.14; confidence interval, 1.02–1.28). One possible explanation for these conflicting results is a differential effect on glucose variability in these studies because this is strongly associated with mortality in this population (48–50). The results of the van den Berghe study showed a substantially lower SD in the intensively treated group (SD of morning blood glucose, 19 *vs.* 33 mg/dl in the intensively *vs.* conventionally treated groups, respectively) as opposed to the NICE-SUGAR study where SD of morning blood glucose was equal in both groups (25 and 26 mg/dl in the intensively and conventionally treated groups, respectively).

We can draw a few conclusions from these studies. First, a relation between short-term glucose variability and microvascular or neurological complications has not been proven in type 1 diabetes patients and has not been investigated in type 2 diabetes. Second, no studies have been performed investigating the influence of glucose variability on macrovascular complications and death in either type 1 or type 2 diabetes patients, but the HEART2D trial suggests that lowering glucose variability does not improve cardiovascular outcome in type 2 diabetes patients after acute myocardial infarction. In contrast, glucose variability is clearly related to mortality in critically ill patients without diabetes, but intervention trials are still lacking.

V. Glucose Variability as a Predictor of Severe Hypoglycemia

Hypoglycemia is a complication of diabetes treatment with sometimes severe consequences, such as seizures, accidents, coma, and death. The frequency of severe hypoglycemia increases exponentially when lowering blood glucose (3). Because lowering blood glucose is the main goal of the treatment of diabetes, occurrence of hypoglycemia is a frequent problem. Much harm could be avoided if it were possible to predict severe hypoglycemia. Unfortunately, only a modest percentage of future severe hypoglycemic episodes can be predicted from known variables such as history of severe hypoglycemia and hypoglycemia awareness (57, 58).

In the search for possible predictors, glucose variability is a plausible candidate because severe hypoglycemia is preceded by blood glucose disturbances (59), and several studies reported a decline in the occurrence of hypoglycemia coinciding with lower glucose variability (60–62). In 1994, Cox *et al.* (63) described glucose variability as a more powerful predictor of future severe hypoglycemia than HbA1c. In this study, 87 type 1 diabetes patients prone to severe hypoglycemia were included. Fifty SMBG readings were collected during 2 to 3 wk, and severe hypoglycemia occurrence was recorded for the subsequent 6 months.

The Diabetes Outcomes in Veterans Study (DOVES) (64) developed and subsequently validated a model for predicting hypoglycemia based on the idea that hypoglycemia is more likely if the mean blood glucose is low or if negative deviations from the mean are large. The 195 insulin-treated type 2 diabetes patients included collected SMBG glucose values four times daily for 8 wk and had three follow-up visits in 1 yr. In this model, the risk of hypoglycemia of any severity (blood glucose ≤ 3.33 mmol/liter) appeared to be unique to each subject and was as much related to glucose variability as to the mean glucose value. The authors suggested that minimizing glucose variability is a plausible method for offsetting the increased risk of hypoglycemia associated with tight glycemic control. Unfortunately, how glycemic variability could be targeted separately remains unclear.

Kilpatrick *et al.* (65) used the datasets of the DCCT to establish whether mean blood glucose and/or glucose variability add to the predictive value of HbA1c for hypoglycemia risk in type 1 diabetes. This is the only study aiming to predict hypoglycemia within 24 h after SMBG collection. In this model, glucose variability, calculated as the SD of daily blood glucose and MAGE, was independently predictive of hypoglycemia just like mean blood glucose. Concerning nighttime hypoglycemic events, variability at the end of the day seemed predictive, suggesting that patients who suffer from this complication could aim at reducing glycemic fluctuations rather than let their blood glucose run higher at bedtime.

From the above, it can be concluded that glucose variability is larger in patients with diabetes who suffer from hypoglycemia, in particular severe hypoglycemia. Also, glucose variability seems a predictor of severe hypoglycemia, but it is more difficult to answer the question whether it is an independent predictor of future hypoglycemia. None of the studies reviewed here performed an analysis to examine whether glucose variability re-

mains a predictor of hypoglycemia when correcting for known predictors such as history of severe hypoglycemia and hypoglycemia unawareness. It may be useful to aim at lower glucose variability in those who suffer from severe hypoglycemia while at the same time trying to prevent a rise in mean blood glucose and HbA1c, but a specific intervention trial is lacking.

VI. Clinical Recommendations

A. Should glucose variability be a target for intervention?

According to the reviewed literature, glucose variability could be investigated as a separate treatment target in nondiabetic, critically ill patients, but with the introduction of strict glucose regulation at the ICU, diminishing hyperglycemic glucose excursions is already a goal of therapy (55, 66). Also, prevention and treatment of hypoglycemia will be a target anyway, although data on whether hypoglycemia in the ICU is related to increased mortality are conflicting (55, 56, 66–70). Glucose regulation with alertness for hypoglycemia should remain the intervention of choice until interventions specifically targeting variability become available and are shown to result in improved outcome.

In insulin-treated diabetes patients with severe hypoglycemia, it is often unavoidable to reduce insulin doses to avoid subsequent episodes. However, a reduction in insulin potentially leads to a deterioration of glucose control (71). Theoretically, therapies specifically aiming to lower glucose variability might prevent severe hypoglycemia while leaving general glucose regulation unaffected. Again, trials supporting this notion are lacking.

As described above, there is little evidence to target glucose variability in general for its limited effects on outcome. But one could think of other reasons to treat glucose variability on an individual basis. It has been shown that within-day variability is an independent predictor of the HbA1c achieved in type 1 diabetes patients receiving multiple daily insulin therapy, with the largest variability correlating with the highest HbA1c levels (72). One of the possible explanations for this is that glucose variability reflects unexpected hypoglycemic episodes due to a variable response to insulin injections. This might lead to patient fear of hypoglycemia and a possible deterioration of glycemic control when avoiding hypoglycemia by resisting raising insulin dosage or physical activity and a subsequent reduction in the patients' quality of life (73). Clinical investigations correlating glycemic variability and quality of life are lacking, however. Another important consequence of large intraindividual glucose variability is that the patient has to perform SMBG more frequently, which is a burden for most diabetes patients both from a psychological and a financial point of view.

B. Available options to target glucose variability

As for outpatients with type 1 or type 2 diabetes, long-acting insulin analogs seem to improve glucose stability; treatment with long-acting analogs has been shown to diminish hypoglycemia and glucose variability (74–76). Prandial insulins, and even more short-acting analogs, diminish postprandial hyperglycemia and consequently glucose variability specifically in type 2 diabetes patients (77, 78). In comparison to the long-acting analog insulin glargine, the glucagon-like peptide-1 receptor agonist exenatide reduced glucose variability with a similar reduction in HbA1c (79). Furthermore, compared with multiple daily insulin injections, the use of continuous sc insulin infusion is in type 1 diabetes associated with a decrease in glucose variability (60, 80, 81). Whether diminishing glycemic variability in these patient groups translates into improved outcome is unknown, although it has been shown that patients with the largest glucose variability benefit the most from switching from multiple daily insulin to continuous sc insulin infusion, achieving significant lower HbA1c values (72).

VII. Conclusions and Future Perspectives

According to the literature we may conclude that glucose variability seems related to oxidative stress in *in vitro* and animal studies and, although not consistently, in an experimental setting in type 2 diabetes patients. In a clinical setting, glucose variability is related to mortality in nondiabetic, critically ill subjects and is associated with (severe) hypoglycemia in insulin-treated diabetes patients. However, at this time there is no supportive evidence for targeting glucose variability separately from mean glucose and/or HbA1c values.

There is no "gold standard" for determining glucose variability. Until added value for other measures is shown, a simple SD seems the best way to quantify glucose variability. CGM readings seem preferable to SMBG measurements to capture all variability, but no data are available comparing these two methods in assessing glucose variability.

The only way to establish the utility of targeting glycemic variability would be further studies specifically aimed at lowering glucose variability to investigate its influence on hard outcomes.

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