Glucose Variability and Diabetic Complications: Is It Time to Treat?

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Increasing evidence is supporting the role of glucose variability (GV) in the development of diabetic complications, particularly cardiovascular (CV) ones (1). Many observational studies (1) and post hoc analyses of trials, such as ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) (2), DEVOTE (Trial Comparing Cardiovascular Safety of Insulin Degludec Versus Insulin Glargine in Subjects With Type 2 Diabetes at High Risk of Cardiovascular Events) (3), VADT (Veterans Affairs Diabetes Trial) (4), ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) (5), and EMPAREG OUTCOME (BI 10773 [Empagliflozin] Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) (6), confirm that in type 2 diabetes long-term GV, in terms of fasting glucose and/or HbA_{1c} variability, is correlated with an increased risk of both CV and microvascular complications. In this issue of *Diabetes Care*, a post hoc analysis of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial adds a further important piece of evidence on this topic (7).

This analysis shows that HbA_{1c} variability is a strong predictor of the total mortality in people with type 2 diabetes and a previous CV event or high risk for CV disease (7). It is worth mentioning that, with abundant measurements in the ACCORD trial, it has been possible for the first time to compare GV effects between the standard and intensive treatment arms.

As is well known, increased mortality from all causes was reported in the intensive treatment arm of ACCORD, leading to the premature discontinuation of the study (8). In this post hoc analysis it emerges that HbA_{1c} variability, together with a higher mean HbA_{1c} level, is involved in the increased total mortality, particularly in the intensive treatment arm (7). The authors suggest that this combination might explain the high total mortality found in this group (7). However, this outcome might have other possible explanations. In ACCORD a high incidence of hypoglycemia was reported in the intensive treatment arm and has been suggested as a possible cause of the increased mortality (9). At the same time, it is well recognized that GV is associated with a high risk of hypoglycemia (10). Therefore, the high total mortality in the intensive treatment arm of ACCORD might be the result of the high incidence of hypoglycemia induced by a high GV. Furthermore, how subjects in the study recovered from hypoglycemia might also be involved: hyperglycemia post-hypoglycemia is also an issue of GV, leading to a dangerous situation linked to the risk of CV complications (11).

Experimental evidence suggests that GV may also produce the phenomenon of so-called "metabolic memory" (12), which cannot be excluded in the clinical setting (13). Recently, it has been suggested that glucose oscillation produces a defective antioxidant response, which in turn results in higher exposure of tissues and cells to oxidative stress, a very well recognized cause of both "metabolic memory" and diabetic complications (14–16). This post hoc analysis (7) evaluates the HbA_{1c} variability only after 8 months from the start of the study. This means that missing the values of GV during the earlier period might have influenced the final outcome.

The study links long-term HbA_{1c} variability to the incidence of total mortality but, unfortunately, fails to clarify the possible role of short-term GV. The issue is that while experimental findings suggest oxidative stress as the possible mechanism linking short-term GV and complications (14–16), the possible mechanisms for long-term GV remain not well defined. It is probable that even though oxidative stress is also generated during long-term GV (17), the quality of care (18) and/or overall medication adherence might play important roles in this case.

A clear difference exists between "short-term" and "long-term" GV (1). Long-term GV is based on visit-to-visit measurements of HbA_{1c} and fasting plasma glucose (1), with the subsequent calculation of their SD and coefficient of variation. Long-term GV partly reflects

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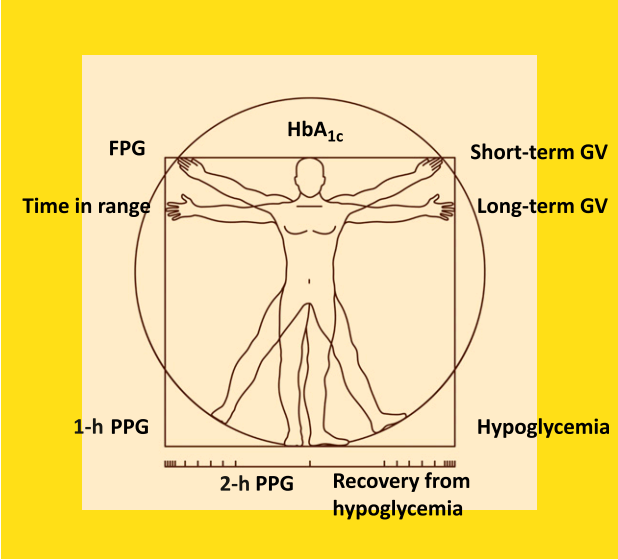

Figure 1—The "perfect" management of hyperglycemia today. A modern "perfect," comprehensive approach to the management of hyperglycemia should consider HbA_{1c}, fasting glycemia (FPG), time in range of glycemia, 1- and 2-h postprandial hyperglycemia (PPG), short- and long-term GV, the risk of hypoglycemia, and the method of recovery from hypoglycemia. The Vitruvian Man, a drawing by Leonardo da Vinci representing the geometry of "perfect" proportions, intended to explore the idea of proportion. The piece is part work of art and part mathematical diagram, conveying the belief that "everything connects to everything else." These concepts have been adopted in the figure to suggest the "perfect" management of hyperglycemia today. (The image used as the basis for development of this figure [Vitruvian Man Vector] was obtained from VectorStock.com.)

the ambient hyperglycemia: it correlates with either mean blood glucose concentrations (19) or mean HbA_{1c} (20). Short-term GV is of increasing concern, expressing the potential risk of episodes of either hyperglycemia or hypoglycemia (10). For many years, short-term GV was calculated from self-monitoring of blood glucose (SMBG) measurements, but this method has been progressively replaced during the last few years by continuous glucose monitoring (CGM) (1). SMBG at best provides an abbreviated diurnal blood glucose profile, whereas CGM with interstitial glucose measurements at 5-min time intervals is a more comprehensive record covering the daytime and nighttime periods and is regarded as the gold standard method for assessing short-term GV. Hopefully, new data on the influence of the "time in range" of glycemia on diabetic complications can contribute to better elucidating the role of short-term GV in the development of those complications (21).

It is often claimed that a specific clinical trial is needed to confirm that reduction in GV results in improvements in diabetic complications. In practice, it would be almost impossible to conduct such a study. The ideal randomized intervention trial for testing the specific impact of the reduction in GV on cardiometabolic risk markers and, beyond that, on hard CV outcomes would require reduction of ambient hyperglycemia to a similar extent in the patients who experienced an improvement of GV and in those who did not. Moreover, one can assume that it would be difficult to conduct a study with CGM over a long period of time, unless wearable devices become available and are accepted by patients for several months or years.

Convincingly, to be used routinely by physicians, information on GV needs to be limited to metrics that can be easily obtained and interpreted. The new technologies will certainly help in improving the management of GV. With the adoption of easier blood glucose monitoring, such as CGM and flash monitoring systems, GV can emerge as an additional glycemic target to consider in daily clinical practice (21).

It is noteworthy that the International Consensus on Use of Continuous Glucose Monitoring has recently integrated a coefficient of variation of $<36\%$ as a key metric of primary GV for defining stable diabetes (22). Finally, the emerging evidence that the 1-h value and the incremental glucose peak during the oral glucose tolerance test can be used as GV indices when CGM is unavailable can further aid in the practical implementation of managing GV (23).

In my opinion, in spite of the limits mentioned above, the mounting evidence requires us to consider managing GV. How? First, by ensuring good quality of care (18). The better the overall quality of care is, the more efficacious the control will be, not only of GV but also of the variability of other risk factors (18). We need to underline that although we pay much attention to GV, there is emerging evidence to suggest that the variability of other risk factors may also be involved in the development of diabetic complications (24). Unfortunately, in the present study (7) the possible role of the variability of the other risk factors has not been evaluated. Furthermore, a therapeutic option might be the use of drugs with good action on GV (1).

In conclusion, is it time to treat GV? It is reasonable that the management of GV has to be part of the more comprehensive approach to the management of hyperglycemia today (Fig. 1). However, I would like to close with a "gloss." In 2005 I suggested, "Correcting the postprandial hyperglycemia may form part of the strategy for the prevention and management of [cardiovascular diseases] in diabetes" (25). It was several years until all the existing guidelines on diabetes management took into consideration the management of postprandial hyperglycemia. The hope is that the process for GV will need less time.

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