Glycemic Variability and Diabetes Complications: Does It Matter? Of Course It Does!

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There is no argument that improving mean levels of glycemic control as judged by assays for glycated hemoglobin (HbA_{1c}) reduces the risks of microvascular complications and cardiovascular disease events in patients with type 1 and type 2 diabetes. However, observations in some trials have suggested that targeting HbA_{1c} to suggested targets may not always result in improved outcomes for people with long-standing type 2 diabetes. The reasons why the glycemic control strategies that primarily use HbA_{1c} in these studies did not have predicted outcomes are not clear. Thus, controversy remains as to whether there are glycemic metrics beyond HbA_{1c} that can be defined as effective measures that can be used in addition to HbA_{1c} to help in assessing the risk of an individual developing diabetes complications. In this regard, the concept of "glycemic variability" (GV) is one metric that has attracted a lot of attention. GV can be simply defined as the degree to which a patient's blood glucose level fluctuates between high (peaks) and low (nadir) levels. The best and most precise way to assess GV is also one that is still debated. Thus, while there is universal agreement that HbA_{1c} is the current gold standard for the primary clinical target, there is no consensus as to whether other proposed glycemic metrics hold promise to provide additional clinical data or whether there should be additional targets beyond HbA_{1c}. Therefore, given the current controversy, we provide a Point-Counterpoint debate on this issue. In the point narrative below, Dr. Hirsch provides his argument that fluctuations in blood glucose as assessed by GV metrics are deleterious and control of GV should be a primary treatment target. In the following counterpoint narrative, Dr. Bergenstal argues that there are better markers to assess the risk of diabetes than GV and provides his consideration of other concepts.

—William T. Cefalu
Editor in Chief, *Diabetes Care*

The long-awaited publication of the Diabetes Control and Complications Trial (DCCT) in 1993 provided the first definitive evidence that "intensive diabetes therapy" could have a dramatic 50–60% reduction in the microvascular complications of type 1 diabetes (1). Although not generally appreciated today, intensive therapy was not defined by the level of HbA_{1c}, although certainly this biomarker was an important end point. Rather, the treatment program was a comprehensive strategy with several components, including multiple injections of insulin (or insulin pump therapy) with prandial insulin adjustment based on the self-monitoring of blood glucose data. What the glycemic "fingerprint" of type 1 diabetes looked like during the DCCT was also not appreciated. With once- or twice-daily insulin administration, glycemic fluctuations were severe (2), but the topic of glycemic variability (GV) was not addressed nor for that matter even considered as a problem.

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The movement to true basal-bolus insulin with multiple injections did not gain momentum in clinical practice until after the introduction of insulin glargine, the first basal insulin analog, in 2001. Although 60% of Americans with type 1 diabetes (not receiving insulin pump therapy) were receiving once- or twice-daily insulin in 1998, this number dropped to 43% in 2003 (3). During this same period, the number of patients injecting insulin four or more times per day increased from 15 to 38%, with increasing numbers switching to insulin pump therapy (3). The overall trend resulted in more physiologic insulin replacement (and presumably less fluctuation of glycemia) for the majority of U.S. patients with type 1 diabetes.

This brings up numerous questions. Was the change to a multicomponent insulin regimen in the DCCT intervention arm at least partially responsible for the dramatic reduction in microvascular complications or was the improvement attributed entirely to the lower HbA_{1c}? Did the ensuing change in philosophy of how to treat patients with type 1 diabetes (and many with type 2 diabetes) alleviate the burden of diabetes outside of the trial? If so, why would the general introduction of prandial insulin at each meal have such a robust impact of clinical outcomes? And finally, is there a causal relationship in the general introduction of prandial insulin resulting in a reduction in the oscillations of blood glucose that could result in a clinical benefit?

Over the years, the issues of glycemia and GV as it pertains to the DCCT have become more complex. First, the treatment group effect explained (only) 6.6% of the variation in risk among subjects, yet virtually all of this effect (96%) can be explained by the differences in HbA_{1c} between the two groups. Second, total glycemic exposure (HbA_{1c} and duration of diabetes) explains only about 11% of the variation in retinopathy risk so that "other factors may presumably explain the remaining 89% of the variation in risk among subjects independent of A1C" (4). There is no controversy that individuals with high HbA_{1c} levels have increased risk of the vascular complications of diabetes; the issue is what other factors may be involved. Given the known negative impacts of both hyperglycemic spikes and hypoglycemia (noted below), it seems plausible that the typical glycemic swings seen in poorly controlled diabetes could be involved in the pathogenesis of the vascular complications of diabetes. Importantly, it is now clear that in type 1 diabetes (with the most severe insulin deficiency and GV) even with HbA_{1c} levels "within target" there is a 2.92-fold increased risk of cardiovascular mortality (5). There is also compelling evidence to suggest that GV, even in those without diabetes, is an independent risk factor for cardiovascular disease (6).

At a cellular level, early work by Ceriello and colleagues (7) reported that human umbilical vein endothelial cells when exposed to variations of glucose concentrations (5 mmol/L and 20 mmol/L) expressed more apoptosis than when only exposed to the higher glucose concentration. There was further clarification in a later study showing that exposure of endothelial cells to both stable and intermittent high glucose stimulates reactive oxygen species overproduction through a protein kinase C–dependent activation of NADPH oxidase, leading to increased cellular apoptosis (8). El-Osta et al. (9) also showed that transient hyperglycemia for 16 h resulted in epigenetic changes in the promoter of nuclear factor-κB subunit p65 in aortic endothelial cells both in vitro and in nondiabetic mice, which cause an increase in p65 gene expression. These epigenetic and gene expression changes persist for at least 6 days of subsequent normal glycemia. The authors concluded that transient spikes of hyperglycemia may be an HbA_{1c}-independent risk factor for diabetes complications. While it is acknowledged that these studies of endothelial cells may not represent GV seen in human diabetes, it was subsequently shown in subjects with type 2 diabetes that with glucose fluctuations there is a "triggering effect" of urinary excretion of 8-iso-prostaglandin F2α, a marker of oxidative stress (10) and endothelial dysfunction (7).

Additionally, it is now becoming clear that many of the cellular processes that occur with hyperglycemic spikes also occur with experimental hypoglycemia. Insulin-induced hypoglycemia has been shown to correlate with increased proinflammatory cytokines, markers of lipid peroxidation, reactive oxygen species, and leukocytosis (11). This suggests that the term "glucose variability" should be qualitatively defined not only as fluctuations of glucose around a mean but also as the deleterious cellular processes attributed to both the hyperglycemic spikes and the hypoglycemic troughs.

There are numerous other clinical clues that GV is involved in the pathogenesis of the vascular complications of diabetes. As the definition of variability includes both glycemic peaks and troughs, the most severe variability with the greatest ranges of blood glucose will include hypoglycemia (12). While there are numerous mechanisms by which hypoglycemia may result in poor macrovascular outcomes (13), hypoglycemia is in fact associated with both macrovascular and microvascular end points in type 2 diabetes (14,15), although the explanation for this is not clear. In type 1 diabetes, severe hypoglycemia is also associated with an increased risk of mortality after a cardiovascular event (16). These data emphasize the significance of hypoglycemia as an aspect of GV.

Perhaps the most compelling illustration of how the change in insulin philosophy has impacted microvascular complications comes from Australia (17). In this analysis of 1,604 adolescents, between 1990 and 2009, retinopathy declined from 53 to 12% ($P < 0.001$), while microalbuminuria was reduced from 8 to 3% ($P = 0.006$). Physiologic insulin replacement (multiple injections and insulin pump therapy) increased from 17 to 88%. Although median HbA_{1c} decreased from 9.1 to 8.5% (76 mmol/mol to 69 mmol/mol) ($P < 0.001$), there was minimum change in the percentage of patients reaching the target HbA_{1c} of less than 7.5% (58 mmol/mol) (Fig. 1).

There are other provocative data supporting GV impacting both macrovascular and microvascular end points. In a prospective and randomized trial, Esposito et al. (18) showed that when subjects with type 2 diabetes were randomized to receiving either glyburide or repaglinide for 1 year, HbA_{1c} reduction was the same in both groups (0.9%), but there was a greater decrease in postprandial hyperglycemia and inflammatory biomarkers with the shorter-acting secretagogue, repaglinide. Importantly,

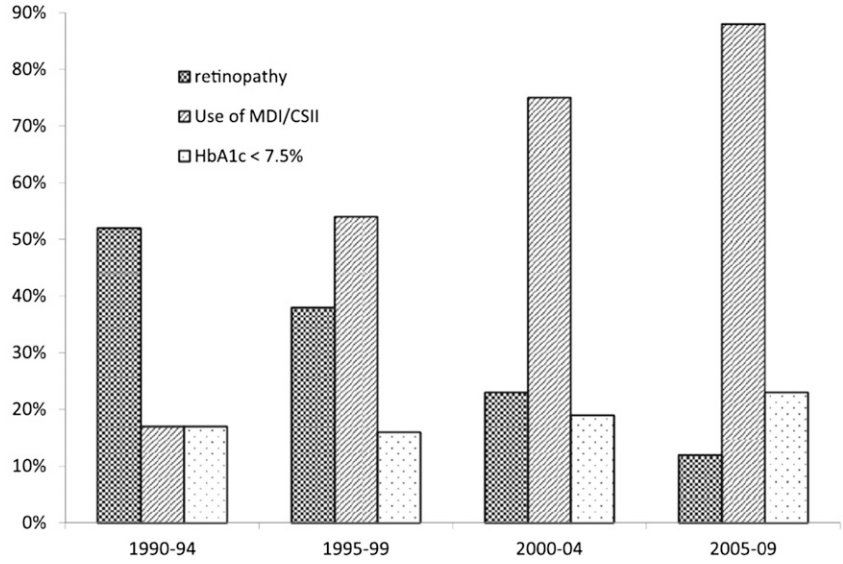

Figure 1—Declining retinopathy in parallel with greater use of multiple daily injections (MDI) and continuous subcutaneous insulin infusion (CSII). Reprinted with permission from Downie et al. (17).

more subjects in the repaglinide group had regression of carotid artery intimal thickness, and this improvement was associated with postprandial, but not fasting, glucose control.

The report often cited as the most important demonstration of no impact of GV on the vascular complications of diabetes comes from Kilpatrick et al. (19). These investigators used capillary glucose profiles from the 1,441 subjects in the DCCT and showed no relationship between GV and diabetic retinopathy or nephropathy (19). Still, this same group did show an association between HbA_{1c} variability and the microvascular complications of diabetes, suggesting that longer-term fluctuations in glycemia seem to contribute to the development of retinopathy and nephropathy (20).

Another important supporting study was a recent publication reviewing the association of 1,5-anhydroglucitol (1,5-AG), a biomarker associated with GV, and outcomes in the Atherosclerosis Risk in Communities (ARIC) Study (21). 1,5-AG is a metabolically inert monosaccharide present in the diet. It competes with glucose for renal reabsorption, and minimal amounts are lost in the urine when blood glucose is below ~10 mmol/L. However, with more profound hyperglycemia, 1,5-AG is lost in the urine as is seen after eating, thus 1,5-AG is a marker of postprandial hyperglycemia and GV. In 12,308 people analyzed (including 958 with diagnosed diabetes) in the ARIC Study, 1,5-AG was associated with prevalent retinopathy. In those with diagnosed diabetes, those with the lowest levels of 1,5-AG (<6 μg/mL, representing the most GV) were 11 times more likely to have retinopathy compared with those with the highest levels of 1,5-AG (>10 μg/mL, representing the least GV). In those with diagnosed diabetes, low 1,5-AG was also associated with a greater than twofold increased risk of incident chronic kidney disease (21). These relationships for the entire study population are shown in Fig. 2. While there are obvious limitations with this retrospective analysis, these compelling data speak to the need for prospective studies to further examine the relationship of GV and the complications of diabetes.

As there is minimal fluctuation of glucose in individuals without diabetes, it is important to ask if more severe glycemic fluctuations may impact depression, quality of life, or other mental health outcomes. This was assessed, and it was shown that in women with type 2 diabetes lower GV was associated with greater health-related quality of life after adjusting for age and weight (22). Furthermore, subjects with higher trait anxiety tended to have steeper glucose excursions (22). How GV may impact central nervous system function deserves further study.

The greatest argument against GV having a role in diabetes comes from the HEART2D (Hyperglycemia and Its Effect After Acute Myocardial Infarction on Cardiovascular Outcomes in Patients With Type 2 Diabetes Mellitus) study (23). These investigators targeted postprandial hyperglycemia (instead of the entire spectrum of GV) and did not show benefit after acute myocardial infarction in subjects with type 2 diabetes using a prandial insulin strategy compared with those using basal insulin (23). This should not be surprising as the difference between daily mean postprandial glucose was only 0.8 mmol/L. One would not expect a difference in cardiovascular events after a myocardial infarction with such a small difference in blood glucose. Furthermore, as we have learned in other trials, our greatest chance for success is in prevention of an initial event, not attempting to change the natural history with established disease.

In the end, there is a biological rationale and enough supporting evidence to endorse the concept that GV is an important risk factor directly involved in the pathogenesis of the vascular complications of diabetes. HbA_{1c}, our first real biomarker of diabetes management, has major limitations and even in the best of circumstances provides only a simplified snapshot of glycemic control (24). The "HbA_{1c} message" is important but incomplete because HbA_{1c} by itself does not explain all of the risk for those who develop the devastating complications of diabetes. While GV is one candidate for an alternative risk factor for vascular complications, there are others, including genetic and environmental risks. This debate will not conclude until a formal, randomized trial examines the relationship between GV and a hard end point, such as retinopathy, nephropathy, or a cardiovascular outcome. A feasibility study to ensure it is possible to randomize a population to two levels of variability by using either a rapid-acting insulin analog or a short-acting glucagon-like peptide 1 receptor agonist with equivalent HbA_{1c} levels will be reported soon, and the design and baseline characteristics of this trial are outlined in this issue of *Diabetes Care*

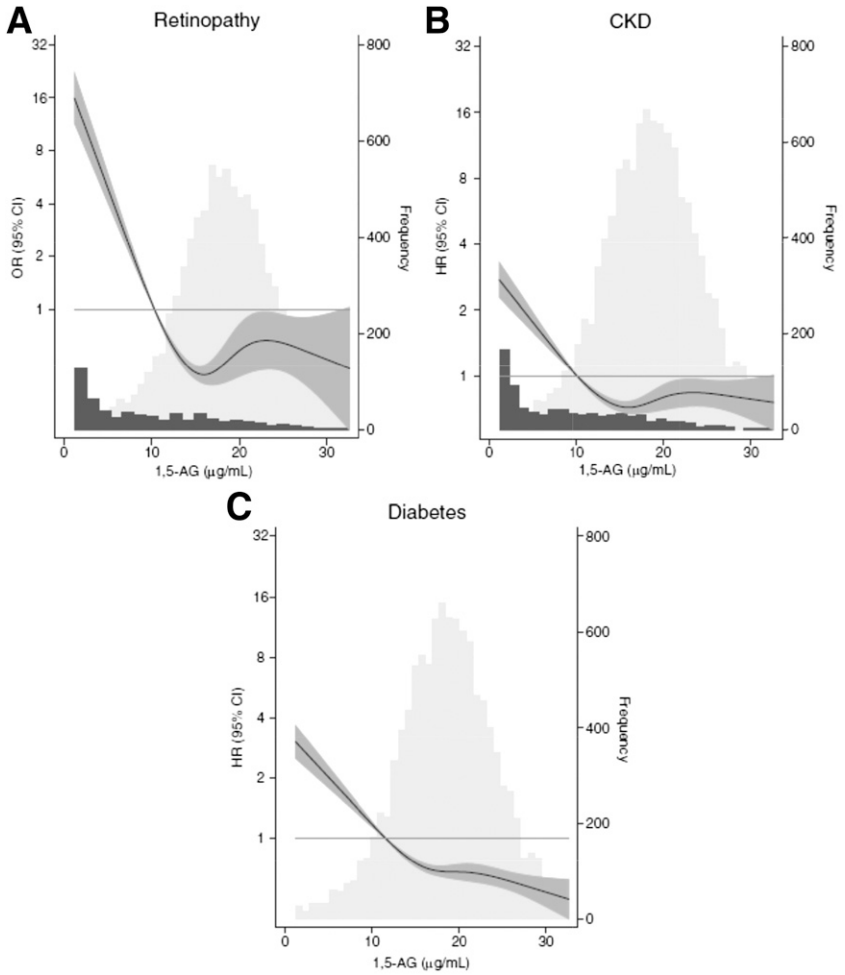

Figure 2—Adjusted associations for baseline 1,5-AG with prevalent retinopathy (odds ratios) and incident chronic kidney disease (CKD) and incident diabetes (hazard ratios) in the overall population of the ARIC Study. Frequency histograms for 1,5-AG are shown separately for people with diagnosed diabetes (dark gray bars) and without diagnosed diabetes (light gray bars). Adjusted odds ratios for prevalent retinopathy are from logistic regression models and adjusted hazard ratios (for incident chronic kidney disease and incident diabetes) are from Cox proportional hazards models. Models were adjusted for age, race, sex, LDL cholesterol, HDL cholesterol, triglycerides, BMI, waist-to-hip ratio, systolic blood pressure, blood pressure–lowering medication, family history of diabetes, education, drinking status, smoking status, and physical activity index. Reprinted with permission from Selvin et al. (21).

(25). Once we can alter variability while maintaining identical HbA_{1c} levels, then we can design an appropriate trial to support the role of glycemic fluctuations. Although it will take a large study of many years to prove this (similar to the DCCT), current evidence supports that fluctuations in blood glucose are dangerous and should be a primary treatment target. This will require the use of newer glucose-lowering agents (such as incretin hormones or sodium–glucose cotransporter 2 inhibitors), faster prandial insulins, and more routine continuous glucose monitoring for both type 1 and type 2 diabetes. It is likely our treatment strategies will be quite different a decade from now once we understand the importance of GV.

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