

# Glycemic Variability: Both Sides of the Story

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## Case for a relationship between postprandial hyperglycemic variability and complication risk

In both type 1 and type 2 diabetes, large prospective clinical studies have shown a strong relationship between time-averaged mean levels of glycemia as measured by HbA<sub>1c</sub> and diabetes complications (1). However, as reviewed elsewhere, in recent years several pieces of evidence have raised the possibility that glycemic instability may also contribute to the development of diabetes complications (2).

Also reviewed elsewhere, in individuals with impaired glucose tolerance the degree of glycemia 2 h after a glucose challenge is a stronger predictor of cardiovascular disease than fasting glycemia (3). In subjects already known to have type 2 diabetes, postprandial glycemia can have the same deleterious effect on the likelihood of developing cardiovascular disease (4). Furthermore, these findings have been supported by pathophysiological evidence demonstrating that acute fluctuations in glycemia can produce significant alterations in normal homeostasis, such as those of endothelial dysfunction and increased inflammation (3). Taken together, these data begin to explain how acute increases in glycemia may influence the development of cardiovascular disease.

However, the concept of glucose variability, even taking the above evidence into consideration, is more complex a phenomenon because it introduces the idea that multiple fluctuations of glycemia in the same individual could be more

harmful than a simple episode of acute hyperglycemia or, indeed, chronic stable hyperglycemia.

**Clinical evidence in diabetes.** An extensive evaluation of this concept has been done by Kilpatrick, Rigby, and Atkin (5), who first reported that glycemic instability is not a predictor of microvascular complications in patients from the Diabetes Control and Complications Trial (DCCT), in particular retinopathy, and then reported that mean daily glucose as well as pre- and postprandial hyperglycemia (PPG) predicted cardiovascular disease in the same cohort (6). Interestingly, the same author more recently reported that HbA<sub>1c</sub> instability, rather than that of glucose, is a predictor of microvascular complications in the same patients (7). The magnitude of the effect of HbA<sub>1c</sub> variability was such that a 1% (11 mmol/mol) increase in HbA<sub>1c</sub> SD was associated with at least a doubling of retinopathy risk and an 80% increase in nephropathy risk. The methodology of these studies, particularly of the first (5), has been largely criticized (8); however, these papers show that the instability of some indices of glycemic control might be deleterious for complications in type 1 diabetes.

Another study (9) followed type 1 diabetic patients over an 11-year period. Onset and progression of micro- and macrovascular complications were recorded and, as expected, these increased over time. Glucose variability (defined as the SD of blood glucose) was calculated from 70 self-monitored measurements

taken over a period of 4 weeks. The study showed that while HbA<sub>1c</sub> was an independent predictor of the incidence and prevalence of nephropathy, SD of blood glucose was found to be a predictor of the prevalence both of peripheral neuropathy and of hypoglycemic unawareness. These data thus suggested that glucose variability may be important in the development of peripheral neuropathy in patients with type 1 diabetes and that the nervous system may be particularly vulnerable to glycemic variability (9).

In type 2 diabetes, the data are less consistent. Several years ago, Mugge et al. (10,11) found in elderly diabetic patients that mortality from all causes (10) and from cardiovascular disease (11) was mainly related to the variability/instability of fasting glycemia rather than to its absolute values. More recently, this finding has been confirmed in a large cohort of >5,000 type 2 diabetic patients (12). Time-dependent variation of fasting glycemia was a strong predictor of all-cause, expanded, and nonexpanded cardiovascular disease–related mortality in these patients, suggesting that glucose variation may become an additional clinical practice goal in the management of these patients (12).

**Basic science evidence.** Several laboratory studies involving both cell lines and animal studies have addressed the issue of “glucose variability.” A deleterious effect of glucose fluctuations on renal mesangial, renal tubulointerstitial, umbilical endothelial, and pancreatic  $\beta$ -cells (2) has been reported. Specifically, mesangial and tubulointerstitial cells cultured in periodic high glucose concentration increase matrix production more than cells cultured in high but stable glucose (2). Increased apoptotic cell death was observed in both  $\beta$ - and endothelial cells in response to fluctuating compared with continuous high glucose (2). Interestingly, in human renal cortical fibroblasts it has been shown that the increased expression of fibrogenesis markers is dependent on high glucose “peaks” but is independent of the total amount of glucose to which cells are exposed (2). Oxidative stress, in particular the increased superoxide production at the mitochondrial level, has been

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suggested as the key link between hyperglycemia and diabetes complications (2). Evidence suggest that the same phenomenon underlines the deleterious effect of oscillating glucose, leading to a more enhanced deleterious effect of fluctuating glucose compared with constant high glucose (2). Finally, more recently it has been reported that exposure to oscillating glucose is more deleterious than constant high glucose and induces a metabolic memory after glucose normalization (13).

Experiments in animals also support the hypothesis of a detrimental effect of fluctuating glucose. It has been demonstrated that repetitive fluctuation in hyperglycemia promotes monocyte endothelial adhesion compared with sustained hyperglycemia (2). Moreover, fluctuations in blood glucose concentrations in atherogenic-prone mice fed maltose accelerated macrophage adhesion to endothelial cells and the formation of fibrotic arteriosclerotic lesions (2). Reducing these glucose “swings” was accompanied by a significant decrease of monocyte endothelial adhesion (2).

All the above laboratory data are consistent with clinical data. Specifically, repeated fluctuations of glucose produce increased circulating levels of inflammatory cytokines compared with stable high glucose in normal subjects and worsened endothelial dysfunction in both normal and type 2 diabetic patients (14). The role of oxidative stress also seems to be a key causative mechanism, since the use of an antioxidant reduced the phenomenon (14). Consistent with the hypothesis of an involvement of oxidative stress is the evidence that in type 2 diabetes daily glucose fluctuations are strongly predictive of increased formation of reactive oxygen species (15). In vivo, however, the situation seems to be even more complex. Marfella et al. (16) recently demonstrated that the major reduction in oxidative stress found after biliopancreatic diversion, compared with diet intervention, seems to be related to the reduction in glucose fluctuations as a consequence of the surgery. Moreover, the biliopancreatic diversion was also accompanied by increased GLP-1 plasma levels after the meal, and, worthy of interest, it has been suggested that GLP-1 may reduce oxidative stress modulating intracellular antioxidant defenses (16).

Glucose variability has been found to be associated with endothelial and cardiovascular damage markers in short-duration type 2 diabetic patients with

optimal metabolic control (17). Oxidative stress was the only independent predictor of increased left ventricular mass and also correlated with glucose variability (17). Consistent with this, it has been reported that oscillating glucose can have more deleterious effects than constant high glucose on endothelial function and oxidative stress—two key players in cardiovascular complications in diabetes in both normal and type 2 diabetic subjects (18).

This hypothesis has recently been tested in clinical trials. It has been reported that blunting glucose variability with DPP-IV inhibitors is accompanied by a decrease of oxidative stress and inflammation (19) and that this effect reduces intima-media thickness progression in type 2 diabetes (20).

With all of these elements taken together, oxidative stress generation appears to be the key player in all of the phenomena reported above, even though the precise mechanism through which oscillating glucose is harmful remains incompletely defined. A possible explanation is that in oscillating glucose conditions, cells are unable to sufficiently increase their own intracellular antioxidant defenses (2), thereby promoting oxidative damage and leading to the development of diabetes complications (2).

### **Case against a relationship between postprandial hyperglycemic variability and complication risk**

While it may seem intuitive that increased glucose variability will lead to acceleration in the development of micro- and macrovascular complications in diabetes, compelling clinical evidence that this is the case remains elusive. Likewise, confirming that PPG (which is a component of glucose variability) also independently leads to more complications is difficult to demonstrate in diabetic populations.

### **Clinical evidence in diabetes**

**Glucose variability and microvascular complications.** In looking to identify a link between glucose variability and microvascular complication risk, the DCCT provides a large dataset on which to test this hypothesis, as it collected seven-point laboratory-measured glucose day profiles every 3 months throughout the study in its 1,441 participants over an average of 6.5 years. It has been found that glucose variability, defined statistically in numerous ways, did not add to mean glucose in predicting the development or progression of retinopathy or nephropathy (5,21). It also showed, in

contrast to a study involving just 100 patients over 4 weeks (9), that there was no evidence that glycemic variability contributed to neuropathy development either (22). A further analysis extended the follow-up into year 4 of the continuation study to the DCCT, the Epidemiology of Diabetes Interventions and Complications (EDIC) study. Again, there was no signal of a contribution of glucose fluctuations toward small vessel complications (23).

There is also a complete paucity of data relating degrees of PPG to the development of diabetes microvascular complications. Indeed, in type 2 diabetes as a whole there are few studies to test the hypothesis that glucose variability contributes to complications. However, in the UK Prospective Diabetes Study (UKPDS) the fact that insulin treatment (where patients are liable to greater glycemic instability [24]) did not seem to confer a higher risk of microvascular disease than oral hypoglycemic agents makes a positive association in type 2 diabetes less likely.

In comparison with this short-term glucose variability, it has proven far less difficult to show an association between HbA<sub>1c</sub> variability and microvascular risk (25). Of course, the timescale of glycemic changes that fluctuations in HbA<sub>1c</sub> reflect is orders of magnitude greater than the within-day fluctuations usually described in relation to glucose variability, and this has given rise to several proposed mechanisms for the observation that are unconnected to glucose variability per se (25). For example, it may be that patients with the largest fluctuations in HbA<sub>1c</sub> are also those with the most haphazard overall diabetes care. However, if long-term glycemic variability were truly to be implicated then a possible mechanism may relate to the observation that acute improvements in HbA<sub>1c</sub> can lead to a short-term “early” worsening in retinopathy before subsequently resulting in a net long-term improvement. If a patient therefore has cycles of HbA<sub>1c</sub> improvement followed by worsening, it is possible that there is insufficient time for them to acquire the long-term complication benefits before they have another cycle of this fluctuant glycaemia.

**Glucose variability and macrovascular risk.** PPG is widely considered to be a marker of increased cardiovascular risk, especially among subjects not already known to have diabetes (3). While PPG is usually regarded as a subset of glucose

variability, it must be highlighted that increased glucose variability need not be a consequence of PPG and that the physiological mechanisms causing glucose excursions can be somewhat different between nondiabetic subjects and those with established diabetes, especially in the case of type 2 diabetes in the context of drug treatment and even more so in type 1 diabetic subjects. However, since the predominant glucose abnormality in the early stages of type 2 diabetes is indeed PPG (3), it would be expected that the main contributor to an increased mean glucose at this point will be PPG. The question therefore arises whether PPG predicts complication risk over and above that which would be envisaged by its contribution to an increased mean glucose for the subject rather than there being any inherent special property to PPG itself or to the glucose variability it promotes.

It is perhaps more than a coincidence that the association between PPG and cardiovascular disease is at its strongest in populations not known to have diabetes (2,3). This may be because it is in these situations that PPG is known to contribute most to mean glucose. In comparison, the evidence that PPG contributes to cardiovascular risk in patients already known to have diabetes is much more limited. The only study to make this claim is the follow-up of the 505 San Luigi Gonzaga type 2 diabetic patients, which found that blood glucose 2 h postlunch was predictive of cardiovascular risk and mortality independently of HbA<sub>1c</sub> (4). However, it is not known whether patients with highest postlunch glucose did indeed have the most variable glucose. Also, it is not possible to tell whether having a high postlunch value was simply the best marker for having the highest mean glucose irrespective of any HbA<sub>1c</sub> result. This latter point is of relevance because an examination of data during the original period of the DCCT found mean glucose to be predictive of cardiovascular events independently of HbA<sub>1c</sub> (6). That study also found neither fasting nor postprandial glucose to preferentially predict cardiovascular risk.

Attempting to reduce cardiovascular risk in diabetes by targeting PPG has also thus far proven unfruitful in patients with diabetes. The Hyperglycemia and Its Effect After Acute Myocardial Infarction on Cardiovascular Outcomes in Patients With Type 2 Diabetes (HEART2D) study specifically targeted PPG (and therefore

glucose variability) in order to reduce cardiovascular events (26). Despite prandial insulin significantly reducing glucose variability compared with patients taking basal insulin (27), the event rate in the patients recruited soon after a myocardial infarction was no different between the treatment arms.

#### Basic science evidence

**Glucose variability and the formation of reactive oxygen species.** While there are many studies that show that glycemic variability can contribute to an increase in the production of free radicals, there are also many others that do not. In contrast to the study by Monnier et al. (15) that showed a close relationship between glucose variability in free-living type 2 diabetic patients and their 24-h urinary excretion of the oxidative stress marker 8-iso PGF<sub>2</sub>α, DeVries and colleagues have shown no such association in either type 2 or type 1 diabetes (28,29). This was despite using a similar study design but with more participants and a wider range of glucose variability and using a more specific method to measure the urinary isoprostanes. Adding to these concerns, it is now also clear that there are potential confounders in using markers such as 8-iso PGF<sub>2</sub>α to represent free radical damage. For instance, Monnier et al. (30) found that insulin treatment, but not oral agents, can lead to a marked reduction in the production of this urinary isoprostane; yet, evidence from studies such as the UKPDS would suggest that oral agents and insulin are equally successful in reducing microvascular risk (31). Lastly, when glucose variability has been artificially adjusted in subjects under the laboratory conditions of glucose clamps there has also been an inconsistency in there being an increase in markers of oxidative stress as a consequence of increasing glucose variability (32).

#### Conclusions

This article brings into focus how the role of glucose variability in the development of vascular complications in diabetes remains unresolved. Translating into hard clinical end points the laboratory evidence that implicates glycemic fluctuations in complication risk has thus far proven difficult. We are also in no position to know whether reducing this variability will lead to a reduction in excess risk—if it exists in the first place. Knowing whether there is benefit in reducing variability beyond that of simply reducing the risk of hypoglycemia is of utmost

importance, as it raises the possibility of allowing patients to help avoid hyperglycemia-related vascular disease without running the same risk of hypoglycemia that a strategy focusing purely on lowering HbA<sub>1c</sub> (by whatever means) might cause. It may therefore guide preferred future therapeutic approaches to treating hyperglycemia.

There are undoubtedly challenges in conducting any interventional trial in diabetes now that standard care already reduces micro- and cardiovascular risk substantially compared with patients from previous generations. With respect to an interventional study specifically designed to address the effect of reducing glucose variability on complication risk, the use of agents such as glucagon-like peptide-1 agonists to reduce glycemic excursions seems particularly attractive, but it will nonetheless be difficult to distinguish whether any positive result was due to reduced variability or an inherent incretin benefit. This means that insulin is likely to remain the cornerstone of any future definitive study. Notwithstanding this, the need for properly powered interventional studies to address this question has never been more important and would mark the answer to one of the largest remaining questions in diabetes.

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