# Glycemic Variability and the Role It Should Play in Diabetes Management and Blood Glucose Monitoring

*a report by*
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Diabetes is estimated to affect 23.6 million people in the US.[1] It is characterized by hyperglycemia, which is partly responsible for the development of diabetic complications such as nephropathy, retinopathy, heart disease, and stroke.[1–3] Glucose levels are generally stable in healthy people; however, they are quite variable in patients with diabetes. This glycemic variability in patients with diabetes involves interprandial hypoglycemia and periods of post-prandial and acute hyperglycemia.[2,4] Factors influencing glycemic variability include deficiency of endogenous insulin and amylin secretion,[5,6] lack of appropriate suppression of glucagon upon eating, poor compliance with diet and exercise therapy,[7] and inappropriate use of exogenous insulin and other hypoglycemic agents.[8,9]

Glycemic variability is typically measured by self-monitoring of blood glucose (SMBG),[10–16] although continuous glucose monitoring (CGM) systems are now a US Food and Drug Administration (FDA)-approved alternative.[17] SMBG is a well-established blood glucose monitoring system[10–16] and can be performed in the clinic or at home.[18,19] It involves intermittent fingerstick measurements to obtain immediate blood glucose values throughout the day.[18,19] Diabetes management software can analyze these data and subsequently calculate the standard deviation (SD) of blood glucose values (the square root of the variance).[20] SD is a measure of glycemic variability, where high SD may indicate several problems, including insulin deficiency or excess, poor matching of calories with insulin, late administration of mealtime insulin (or missing injections completely), erratic snacking, the need for insulin pump therapy, etc.[4] SMBG also allows identification of abnormal glucose values, such as hypo-(nadir) and hyperglycemic (peak) periods.[16,17] Thus, the use of SMBG along with this software would allow patients to modify their treatment regimen and obtain better glycemic control.[17,21] The ideal target SD is: SD x 3 < mean glucose; however, this target is hard to achieve in type 1 diabetes.[4] A simple target to strive for is: SD x 2 < mean glucose.[4] On the other hand, the relatively new CGM devices involve continuous glucose monitoring of interstitial fluid,[17] which can be used to calculate the mean amplitude of glucose excursion (MAGE), representing intraday glycemic variability,[17] and mean of the daily differences, representing interday variability.[22] CGM use in type 1 diabetes is becoming more common; however, very little data on its use in type 2 diabetes have been published.

Diabetes management has evolved from the days of bovine and porcine insulin, with the introduction of rapid- and long-acting analogs of human insulin that provide a better simulation of endogenous insulin levels for diabetic patients using insulin. Patients with type 2 diabetes are now served by an increasing variety of oral antidiabetic agents, with many of the newer agents having the advantage of being glucose-dependent in their mechanism of action, thus reducing the risk for hypoglycemia and, thereby,

glycemic variability. Hyperglycemia is established as a risk factor for diabetes-related complications,[11] and the comprehensive Diabetes Complications and Control Trial (DCCT)[11,20] and United Kingdom Prospective Diabetes Study (UKPDS)[23] have established the long-term benefits of intensive glycemic control for reducing the risk for microvascular complications. Since glycated hemoglobin ($HbA_{1c}$) is a marker of glycemia,[24–26] the American Diabetes Association's (ADA's) current recommended treatment target is to achieve a $HbA_{1c}$ level <7%,[27] with the goal of achieving near-normoglycemia without hypoglycemia.[28] There is mounting evidence that glycemic variability is linked to long-term diabetic complications,[4] which would appear to necessitate a review of current diabetes management regimens. This article examines the latest evidence and also discusses the role of glycemic variability in diabetes management and blood glucose monitoring.

## Glycemic Variability—A Risk Factor for Diabetes Complications?

While hyperglycemia is known to be a risk factor for diabetes-related complications, the role of glycemic variability is not fully understood.

### In Vitro *Evidence*

It is well-established that the pathophysiology of diabetic complications involves hyperglycemia-induced oxidative stress and excessive glycation.[2,20] Oxidative stress results from the overproduction of reactive oxygen radicals (ROS).[4] The effect of glycemic variability on ROS levels has been investigated in cell cultures and in patients with type 2 diabetes.[29,30] Risso et al. demonstrated that in human umbilical vein endothelial cells (HUVECs) there was a marked increase in cellular apoptosis when they were cultured with an intermittent high-glucose medium than with a constantly high-glucose medium.[29] Quagliaro et al. also investigated the effect of culture using an intermittent

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high-glucose medium versus constant high-glucose medium on high-glucose-ROS generation in HUVECs.[30] Since ROS cannot be directly measured,[20,31] they used the oxidative products 8-hydroxydeoxyguanosine (8-OHdG)[32,33] and nitrotyrosine as markers of ROS levels.[34] There was a greater production of both 8-OHdG and nitrotyrosine in cells cultured in the intermittent glucose medium. These *in vitro* data show that glycemic variability may have a role in the development of diabetic complications.

NF-κB activation and signal transduction are intrinsic to the development of diabetic complications.[35] Schiekofer et al. investigated the effect of changes in glucose levels on the activation of NF-κB in peripheral blood mononuclear cells of healthy volunteers.[35] They observed an increase in NF-κB activation when glucose was raised from 5 to 10mM, with or without insulin, over two hours. These data suggest that even acute (short-term) changes in blood glucose may be involved in the development of diabetic complications.

### Human Clinical Evidence

The DCCT trial evaluated the effect of intensive treatment on the development and progression of long-term complications in type 1 diabetes.[11] This was a nine-year follow-up study of 1,441 individuals with type 1 diabetes in which patients were randomly assigned to intensive or conventional treatment. The risk for retinopathy at an $HbA_{1c}$ level of 9.0% was found to be reduced by more than 50% in the intensive group versus the conventional group.[4,36] This difference has been attributed to the lower intraday glycemic variability in the intensive group, which received prandial insulin injections at meals along with once- or twice-daily basal insulin, whereas the conventional group received only two injections per day.[2,36] However, a more recent analysis suggests that this difference in the risk for retinopathy may be due to an artifact in the assumptions used in the statistical model and that most of the reduction in complications seen in the intensive arm of the DCCT can be explained by the reduction in $HbA_{1c}$ alone.[37] Others have analyzed the seven-point glycemic profiles taken every three months from the DCCT[38] and found that acute (intraday) glucose variability was not linked to microvascular complications. However, Monnier and Colette argue that since Kilpatrick et al. calculated the variability as the SD around the mean of a seven-point glycemic profile measured every three months, the major excursions may have gone unnoticed.[2] This may have led Kilpatrick et al. to discount the role of fluctuations in the risk for developing complications.[2] In 2007, Kilpatrick et al. published another analysis of the seven-point SMBG profiles obtained every three months from the DCCT subjects and showed that mean blood glucose and glycemic variability independently predicted severe hypoglycemia.[39] In 2008, they published a further study analyzing the effect of long-term glycemic variability of $HbA_{1c}$ on the risk for developing microvascular complications in the DCCT.[40] They found that $HbA_{1c}$ variability was greater in the conventionally treated group than in the intensive group ($HbA_{1c}$ SD 0.86 and 0.59, respectively), and the risk for complications was greater when the effects of mean $HbA_{1c}$ and $HbA_{1c}$ variability were combined as opposed to using mean $HbA_{1c}$ alone. These data suggest that long-term glycemic variability may be an additional risk factor for the development of microvascular complications.[40]

Monnier et al. have investigated the effect of sustained chronic hyperglycemia and acute glycemic variability on oxidative stress in patients with type 2 diabetes and poor glycemic control who were not using insulin.[41] MAGE was used as a measure of acute glycemic variability.[41] They showed that free radical production measured by 24-hour urinary excretion of isoprostanes (8-iso-prostaglandin $F_{2\alpha}$) was higher in patients with type 2 diabetes than in healthy

controls and, furthermore, that glycemic variability was strongly correlated with urinary excretion of the free radicals. The results of this study add to the findings by Shiekofer et al. in showing that acute glycemic variability may be a risk factor for diabetes complications. Thus, both acute and long-term glycemic variability independent of mean blood glucose levels seem to be additional risk factors for the development of microvascular complications. One of the mechanisms of action appears to be the overproduction of free radicals caused by both acute and chronic changes in glycemia.[40] In addition to a risk for microvascular complications, Prince et al. have shown that glycemic variability may also be a risk factor for the development of macrovascular complications in patients with type 1 diabetes.[42] The Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) epidemiological study showed that there was a strong association between greater glycemic variability and a higher risk for macrovascular disease.[43] Randomized clinical trials are needed to further evaluate the exact role of glucose fluctuations in the development of long-term complications in patients with diabetes. It should be noted that three recent major trials have studied the effect of intensive glycemic control on cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease or significant cardiovascular risk factors. The two completed trials, ADVANCE[44] and the Veterans Affairs Diabetes Trial (VADT),[45] showed no significant reduction in cardiovascular outcomes with intensive glycemic control, while the third trial, ACCORD,[46] terminated its glycemic control study early due to increased mortality in participants randomized to the very intensive glycemic control strategy. However, it is important to mention that the lack of meter glucose download data and glycemic variability data in these major trials makes it difficult to make any assumptions on why the intensive control group in these studies did not show a significant reduction in the combined composite of death, non-fatal myocardial infarction (MI), and stroke in spite of improved glycemic control. Furthermore, it has been suggested that severe hypoglycemia may have played an important role in causing increased mortality in the intensive group of the ACCORD participants as well as in some of the participants in the conventional arm of the VADT.[47]

### Role of Glycemic Variability in Diabetes Management

Glycemic management of diabetes should focus on achieving near-normoglycemia without hypoglycemia,[28] thereby reducing the risk for complications.[1,3,23,48] Since glycemic variability may be a risk factor for diabetes-related complications, it is strongly suggested that new diabetes management strategies include minimizing glycemic variability.[2,4] New treatment strategies are increasingly focusing on reducing post-prandial glycemic excursions as well as $HbA_{1c}$ levels to reduce the risk for long-term complications.

Minimizing glycemic variability may be a valuable strategy. This hypothesis is supported by a study by Zhou et al., who investigated the effect of intensive treatment with flexible multiple daily injections of insulin on blood glucose variability in patients with type 2 diabetes.[28] Intraday, interday, and post-prandial blood glucose variability was monitored using the continuous glucose monitoring system, and intensive treatment significantly decreased all three of these blood glucose variability measurements. Iatrogenic hypoglycemia is often an issue in both type 1 and type 2 diabetes,[23,49] and studies should determine the best pharmacological strategy to reduce glycemic variability while ensuring the absence of hypoglycemia.[28] A successful strategy to minimize glycemic variability in type 2 diabetes may involve the use of newer agents such as glucagon-like peptide (GLP)-1 agonists and dipeptidyl peptidase (DPP)-4 inhibitors that secrete insulin and suppress glucagon in a glucose-dependent manner, controlling post-prandial glucose excursions as well as lowering overall

glycemia without the increased risk for hypoglycemia. Heine et al. treated patients with suboptimally controlled type 2 diabetes with an injection of either insulin glargine (once-daily) or the GLP-1 agonist exenatide (twice daily).[50] Changes in glycemic excursions from baseline to end-point were determined by reading the crude difference between post-prandial peaks and interprandial nadirs on the mean glucose patterns. Glargine reduced fasting glucose concentrations to a greater extent than exenatide, while exenatide reduced post-prandial variability to a greater extent than glargine. Even though the $HbA_{1c}$ reduction in both groups was the same, exenatide reduced glycemic excursions by around 50% at the end-point compared with baseline. This indicates that the use of exenatide may be appropriate in treatment strategies that aim to reduce post-prandial excursions and thus glycemic variability.

In insulin-requiring patients, insulin analogs may also be used to reduce glycemic variability. Such insulin analogs include the rapid-acting insulins lispro, aspart, and glulisine, which have a more rapid onset, greater peak, and shorter duration of action than regular human insulin.[51] These rapid-acting insulin analogs should be administered within 15 minutes of meal consumption.[52] It has also been shown that these newer insulin analogs reduce the risk for hypoglycemia both during the day and nocturnally compared with regular human insulin.[51,53,54] These rapid-acting insulin analogs may also be useful in patients experiencing periods of acute hyperglycemia. To address the basal fluctuations in glycemia during the day, one strategy might include administration of long-acting insulin analogs, such as insulin detemir and insulin glargine.[51] These insulins have prolonged activity, a relatively flat time–action profile, and more consistent absorption.[51] One study investigated the effect of insulin detemir and neutral protamine Hagedorn (NPH) in patients with type 2 diabetes, where insulin was titrated weekly to achieve a target fasting plasma glucose and pre-supper glucose levels ≤108mg/dl.[55] This study showed that less glycemic variability occurred with determir compared with NPH, and this has been confirmed by other studies.[55–58] Another strategy to minimize glycemic fluctuations (fasting and post-prandial) during the day is the administration of multiple injections of rapid-acting insulin analogs for prandial control along with basal insulin. In conclusion, the new insulin analogs are more physiological and conveniently dosed and reduce the potential for hypoglycemia, so there is now the possibility of achieving better glycemic control and subsequently reducing the risk for long-term complications.[52] Future studies are needed to determine the best pharmacological strategies for minimizing glycemic variability and the increased free radical production it causes.[59]

### Self-monitoring Blood Glucose in Diabetes Management

Diabetes management requires frequent blood glucose monitoring,[16,60] which is achieved using blood glucose monitoring devices.[16] SMBG is a cornerstone of diabetes management, particularly in those with type 1 diabetes[10–12] and patients with type 2 diabetes using insulin.[12–16] It has been suggested that since glycemic variability seems to be a risk factor for diabetic complications, it should be monitored through SMBG or CGM.[20,59,61,62] This would allow modification of the treatment strategy to minimize glycemic variability, thereby lowering the risk for complications.[12] The daily use of SMBG along with the diabetes management software can reveal the immediate effect of patient behavior (such as eating, physical activity, and medication) on glucose levels[19] and allow modification of the treatment strategy to minimize glycemic variability,[20] potentially reducing the risk for complications.[20] In patients with diabetes receiving insulin therapy who have glycemic variability (as determined through SMBG), the glucose fluctuations can be minimized by altering the

timing, dosage, or frequency of insulin injections.[12] In treating patients with diabetes, it might be helpful to draw up a written schedule of glycemic goals corresponding to stepwise interventions in insulin dosing and timing of meals that are reviewed and adjusted at regular intervals, allowing modification of treatment strategies to minimize glycemic variability and, thereby, improve diabetes management.[18]

The contribution of post-prandial excursions to glycemic variability is evident. Post-prandial glycemia can be monitored using SMBG or CGM to help achieve a more physiological glycemic profile.[17] It is suggested that patients with diabetes check their glycemia at least four times a day (before meals and at bedtime) with a blood glucose meter, with additional measurements if they experience symptoms of hypo- or hyperglycemia or the $HbA_{1c}$ is not at goal in spite of acceptable control before meals and at bedtime.[17] The ADA has recommended SMBG three or more times daily for patients with type 1 diabetes, but no specific frequency has been recommended for patients with type 2 diabetes who are not on insulin.[27] A recent meeting of a group of experts suggested that patients with type 2 diabetes should base the frequency of glucose monitoring on the extent of diabetes progression and insulin deficiency and the treatment modalities used.[18]

It should be noted that SMBG is associated with a few limitations. Its clinical value in patients who are not treated with insulin needs to be fully evaluated.[21] SMBG has been associated with patient compliance issues,[16,17] but technological improvements to the blood glucose monitors have decreased the non-compliance.[16] The use of CGM devices in type 1 diabetes has been validated,[63] but its benefit and use in type 2 diabetes management is unknown. SMBG is still a mainstay in diabetes management as it provides detailed information about the quality of glycemic control and thereby allows better diabetes management.[12]

### Conclusions

Diabetes is characterized by sustained chronic hyperglycemia and glycemic variability. Traditionally, diabetes management has focused on achieving normal plasma glucose levels as chronic hyperglycemia is a risk factor for long-term complications. Recent studies have suggested that glycemic variability may be an additional risk factor for the long-term complications of diabetes. Thus, new diabetes management strategies should also focus on minimizing glycemic variability. Strategies to minimize glycemic variability may include intensive therapy with multiple insulin injections, the use of rapid-acting insulin analogs to reduce periods of acute hyperglycemia, or the use of long-acting insulin analogs to minimize basal or fasting blood glucose variability. The new insulin analogs may help achieve better glycemic control and further reduce the risk for long-term complications. New oral and subcutaneous antidiabetic agents may be used to reduce glycemic variability in patients with type 2 diabetes not using insulin. A fundamental part of diabetes management is SMBG using blood glucose monitoring devices. Diabetes management software can use the data from SMBG to give a measure of glycemic variability. The use of SMBG along with this software will allow the patient to monitor glycemic excursions and identify any effect of behavior or treatment schedule on glycemic variability and control. If needed, the patient can then adjust the treatment regimen or behavior to minimize glycemic variability and, potentially, reduce the risk for diabetic complications. Large-scale studies are needed to validate the impact of reducing glycemic variability with these new treatment strategies, and monitoring systems will in fact reduce long-term complications of diabetes. ■

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