

## In Brief

Hyperglycemia in diabetes is known to be associated with both micro- and macrovascular complications. However, multiple studies have raised the question of whether variation in glucose levels, in addition to average glucose, might be a risk factor for these complications. This article summarizes the available data on glycemic variability and how they might contribute to complications in both type 1 and type 2 diabetes.

# Glycemic Variability: Looking Beyond the A1C

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Hyperglycemia in both type 1 and type 2 diabetes is associated with diabetes complications, including retinopathy, nephropathy, and cardiovascular disease (CVD). Clinicians typically gauge glycemic control with A1C, which reflects the average glucose level over the previous 2–3 months. However, a number of studies<sup>1–4</sup> have questioned whether, in addition to average glucose, glucose variability could be an independent risk factor for diabetes complications.

The Diabetes Control and Complications Trial (DCCT)<sup>5</sup> studied the effect of intensive versus conventional insulin therapy on the occurrence and progression of microvascular complications in patients with type 1 diabetes. The results showed a 50% relative risk reduction in retinopathy, nephropathy, and neuropathy in the intensively treated group, which could largely be explained by improvements in A1C. However, when patients from different treatment groups at the same A1C level were compared, those in the conventional group had higher rates of complications, suggesting that factors other than the average blood glucose level were contributing to the risk of complications.<sup>6</sup> Subsequent analysis of the DCCT data found this initial finding to be erroneous, and reanalysis found 96% of the treatment group effect was in fact due to A1C.<sup>7</sup> However, the authors concluded that total glycemic exposure, a composite of A1C and duration of diabetes, only accounted for 11% of the difference in

retinopathy risk for the entire cohort. Thus, factors other than average blood glucose may contribute to the development of diabetes complications.

Patients with similar A1C values can have dramatically different glucose profiles. Some patients have minimal glucose excursions, with little variation from preprandial to postprandial glucose levels and rare hypoglycemia. Other patients have widely fluctuating glucose levels, with frequent episodes of hypoglycemia and marked postprandial increases in blood glucose.

These changes in blood glucose over time reflect glucose variability. Glucose variability can be described as within-day variability, with differences between fasting and postprandial blood glucose values throughout 24 hours, and between-day variability, reflecting differences in blood glucose control from day to day. This glucose variability is not reflected in A1C and thus may represent an additional risk factor for the development of diabetes complications.

Because A1C reflects average glucose level but not variability, measuring glucose variability requires other methods for analysis. A number of measurements have been developed for clinical use. The most practical for outpatient use is the standard deviation (SD) calculated from self-monitoring of blood glucose (SMBG) values. This can be calculated from patients' blood glucose meter downloads and provides a measure of glucose variability over a certain

period of time, typically 1–3 months. The software can also provide information about the SD of fasting and postprandial glucose values.

More frequent glucose trends are available with the use of continuous glucose monitoring (CGM) devices. With more data points, it is possible to calculate the mean amplitude of glucose excursions (MAGE), which is a measure of within-day glucose variability. MAGE reflects the average difference between consecutive blood glucose values that are more than 1 SD from the daily mean. For between-day variability, the mean of daily differences (MODD), which is the average of the difference between blood glucose values measured at the same time on consecutive days, can be used (Table 1).<sup>8</sup> There is a high degree of correlation with SD and both MAGE and MODD.<sup>9</sup> Whichever method is most convenient for patients and providers can reasonably be used to measure glucose variability.

There remains some controversy as to how glucose variability could contribute to diabetes complications. Multiple *in vitro* studies with human cell lines have shown that intermittent high glucose levels induce more oxidative stress than continuous high glucose.<sup>1</sup> Animal studies have confirmed these studies, showing greater impairment in endothelial function for untreated diabetic rats (continuous high glucose) versus rats having intermittent insulin treatment (variable glycemia).<sup>10</sup> Human studies, however, are less clear, with some researchers finding a correlation between oxidative stress and glucose variability,<sup>11,12</sup> but others failing to confirm these findings.<sup>1,13</sup>

Although *in vitro* data support the oxidative stress theory, *in vivo* stud-

ies leave some uncertainty about how glycemic variability can contribute to diabetes complications. However, multiple studies do support the idea that variations in glucose levels are an important factor in the development of diabetes complications.<sup>4</sup>

Using different methods for analyzing glucose variability, there is some support for a correlation between glucose variability and diabetes complications in patients with type 1 diabetes. Multiple analyses of the DCCT data have used the seven-point daily glucose profiles to measure within-day glucose variability using SD and MAGE.<sup>14,15</sup> They found no relationship between glucose variability and microvascular complications during the initial DCCT or during 4 years of follow-up.<sup>16</sup> However, in this same population, when glucose variability was measured as the SD of A1C during the 9-year follow-up period, there was a significant relationship with the development of both retinopathy and nephropathy.<sup>17</sup> This suggests that long-term glucose variability, over months to years, may be a more important risk for development of microvascular complications than blood glucose variability within a given day.

The relationship between glucose variability and neuropathy has also been looked at by several groups. Analysis of the DCCT dataset found no relationship between same-day glucose variability and neuropathy, whether measured by MAGE or SD.<sup>18</sup> Another small study of patients with neuropathy<sup>19</sup> similarly did not find an association between MAGE and onset or progression of neuropathy. However, patients who suffered from painful neuropathy had more frequent glucose excursions, suggest-

ing a relationship between glycemic variability and pain symptoms. In a separate study looking at long-term glucose variability reported as the SD of 4-week blood glucose data,<sup>20</sup> glucose variability was predictive of the prevalence of peripheral neuropathy during 11 years of follow-up. There was no relationship with retinopathy or nephropathy. These studies again suggest that it is not the glucose variability in a given day, but rather variability over time that is a risk factor for microvascular and neuropathic complications of diabetes.

Although there have been many studies looking at microvascular complications and glucose variability in patients with type 1 diabetes, there are few data to suggest a relationship between glucose variability and CVD in these patients. Analysis of the DCCT data showed no relationship between within-day glucose variation and cardiovascular events.<sup>21</sup> Another study<sup>22</sup> found no relationship between within-day glucose variability and arterial stiffness, a marker for cardiovascular risk. A third study<sup>23</sup> looked at coronary calcium scores as a marker for CVD. The researchers found glucose variability over 3–5 days of CGM, measured by SD, was positively associated with coronary artery calcium score in men with type 1 diabetes. There was no association for women. More research is needed to clarify the relationship between glucose variability in type 1 diabetes and CVD.

Among patients with type 2 diabetes, there is more evidence to support a relationship between both fasting and postprandial glucose variability and cardiovascular risk. In a study of 300 patients with type 2 diabetes who presented with chest pain,<sup>24</sup> within-

**Table 1. Measurement of Glycemic Variability**

Measure	Type of Variability	Method of Calculation	Notes
SD	Intra- or between-day	Deviation from the mean	<ul style="list-style-type: none"> <li>Easily calculated from in-office downloads of SMBG or CGM</li> </ul>
MAGE	Intra-day	Average difference between consecutive blood glucose values	<ul style="list-style-type: none"> <li>Widely used with CGM data in studies</li> <li>Requires software for the calculations</li> <li>Arbitrary definition of peaks and nadirs</li> </ul>
MODD	Between-day	Average difference between glucose values at the same time on consecutive days	<ul style="list-style-type: none"> <li>Requires large number of data points and software to perform the calculations</li> </ul>

day glucose variability was associated with the presence and severity of coronary artery disease. Postprandial glucose excursions have been found to be associated with increased carotid intima media thickness (CIMT),<sup>25</sup> as well as cardiovascular events.<sup>26</sup> Variability of fasting plasma glucose in elderly patients (> 75 years of age) with type 2 diabetes was linked to an increase in overall mortality and specifically predicted cardiovascular death.<sup>27,28</sup> A similar analysis of younger patients, aged 56–74 years, found that variability of fasting glucose was an independent predictor of total and cardiovascular mortality during the subsequent 10 years among this population with type 2 diabetes.<sup>29</sup> Together, these studies suggest that glycemic variability is an independent risk factor for the development of atherosclerosis, but the mechanism remains unclear.

With respect to microvascular complications and type 2 diabetes, there are conflicting results regarding the relationship to glucose variability. One study found that fasting glucose variability did predict the development of retinopathy in patients with type 2 diabetes during 5 years of follow-up.<sup>30</sup> A second group, looking at development of retinopathy during 30–40 years of follow-up, confirmed the relationship between fasting glucose variability and both nonproliferative and proliferative retinopathy.<sup>31,32</sup> A third group, however, found that only the magnitude of hyperglycemia, and not variability, predicted the development or progression of retinopathy during the subsequent 4 years.<sup>33</sup> This study, however, looked at an elderly population with an average duration of diabetes of 20 years during 4 years of follow-up, whereas the previous studies included younger patients with shorter durations of diabetes, making it difficult to compare the results of the different studies. The effects of glucose variability on nephropathy and neuropathy in patients with type 2 diabetes are not well described.

Although there have not been any interventional studies looking at the effects of decreasing glucose variability on outcomes in patients with type 1 diabetes, there have been several studies looking at cardiovascular outcomes in patients with type 2 diabetes. A meta-analysis<sup>34</sup> of seven studies looking at the effects of acarbose, which decreases postprandial glucose excursions,

on cardiovascular outcomes found a significant decrease in the incidence of myocardial infarction with a minimum of 52 weeks of acarbose treatment (range 52–164 weeks). Another study<sup>35</sup> using repaglinide to decrease postprandial glucose versus glyburide, which decreases fasting plasma glucose, showed a decrease in CIMT in the repaglinide group, despite similar improvements in A1C in both groups. Yet another study<sup>36</sup> failed to find an effect of postprandial versus fasting glycemia targets in preventing CVD, but this study failed to achieve its specified blood glucose targets or event rate, so it may not have been properly powered to detect a difference. Larger clinical studies are needed to determine whether decreasing glucose variability will improve clinical outcomes.

In addition to the micro- and macrovascular complications of diabetes, glycemic variability may also affect psychological outcomes. One small study<sup>37</sup> of patients with type 1 diabetes found high glucose values (> 180 mg/dl) to be associated with negative mood ratings, including tension, anhedonia, and decreased arousal, although no association was seen with between-day glucose variability. Another study<sup>38</sup> of 60 patients with type 2 diabetes found that negative mood (depression, anxiety) and cognitive symptoms (difficulty concentrating, slowed thinking) were associated with a change in blood glucose after a meal, suggesting that within-day glucose variability can negatively affect an individual's mood and psychological well-being.

Within-day glucose variability is also tied to hypoglycemia in both type 1 and type 2 diabetes.<sup>39,40</sup> This includes asymptomatic hypoglycemia,<sup>41</sup> which can have a significant impact on a patient's daily life. These studies suggest that glycemic variability not only has the potential to affect long-term vascular complications, but also can affect quality of life on a day-to-day basis.

A1C testing remains the standard of care for managing diabetes, but there is growing evidence that A1C does not reflect the complete picture. Glycemic variability is another factor that likely contributes to complications of diabetes, including negative effects on mood and cognition, as well as the risk of hypoglycemia. Although there are not yet enough data to offer

guidelines for glycemic variability, a good rule of thumb is an SD that is less than half of the average blood glucose level. At this level, both hyper- and hypoglycemia are minimized. It remains unclear whether interventions to decrease glycemic variability lead to improved outcomes, but clinicians should be aware of glycemic variability in managing their patients. It is important to recognize that despite having a “normal” A1C, patients may not have optimal control of their diabetes, as illustrated by the following case.

### Case Study

You receive your “report card” from an oversight insurance management agency group. The report includes your patient A, a 56-year-old woman with type 2 diabetes with an A1C of 7.2%. The report also includes patient B, a 56-year-old woman with an A1C of 6.6%. Patient A has an average glucose on glucose meter download of 150 mg/dl over the past month, with an SD of 36 mg/dl. Patient B also has an average glucose on the past month's download of 150 mg/dl, but her SD is 100 mg/dl. Her family calls you almost monthly to report an incident of hypoglycemia requiring assistance and to say they are quite concerned about leaving her alone at any time of the day because she is unable to feel symptoms of hypoglycemia. The oversight insurance company commends you on the A1C of 6.6%, but urges you to be more aggressive with your patient with the A1C of 7.2%.

Which patient has the better glucose control? And which patient might have fewer glycemic sequelae? Which patient is likely to have less hypoglycemia and to feel better?

In patient B, with the lower A1C of 6.6%, the blood glucose meter download shows a considerable amount of glucose variability, with a high SD. This suggests an extensive glucose range, with frequent hypoglycemia and episodes of hyperglycemia. The patient reports fatigue and depression, and her family expresses concerns about her safety. In addition, patient B may be at greater risk for cardiovascular mortality related to glycemic variability, despite having the lower A1C.

Patient A has an A1C higher than the “ideal” A1C target. However, her glycemic variability is much less than for patient B. She has infrequent hypo-

glycemia, which is easily recognized and treated. Her quality of life is less affected by her diabetes, and she is less likely to suffer long-term complications. Despite having the lower A1C, patient A is suffering more adverse effects from her diabetes, in large part because of her increased glycemic variability.

Although A1C is the current standard for defining optimal glycemic control, it is clear that not all A1Cs are equal. Glycemic variability is another factor clinicians should consider when managing patients' diabetes because it could affect not only cardiovascular and microvascular outcomes, but perhaps more importantly for patients, quality of life.

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