Glycemic Variability: Assessing Glycemia Differently and the Implications for Dietary Management of Diabetes

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Abstract

The primary therapeutic target for diabetes management is the achievement of good glycemic control, of which glycated hemoglobin (HbA1c) remains the standard clinical marker. However, glycemic variability (GV; the amplitude, frequency, and duration of glycemic fluctuations around mean blood glucose) is an emerging target for blood glucose control. A growing body of evidence supports GV as an independent risk factor for diabetes complications. Several techniques have been developed to assess and quantify intraday and interday GV. Additionally, GV can be influenced by several nutritional factors, including carbohydrate quality, quantity; and distribution; protein intake; and fiber intake. These factors have important implications for clinical nutrition practice and for optimizing blood glucose control for diabetes management. This review discusses the available evidence for GV as a marker of glycemic control and risk factor for diabetes complications. GV quantification techniques and the influence of nutritional considerations for diabetes management are also discussed.

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INTRODUCTION

Diabetes prevalence has reached epidemic proportions. Approximately 387 million people worldwide have diabetes, with type 2 diabetes mellitus (T2DM) accounting for over 90% of cases. According to the International Diabetes Federation (110), an estimated 1 in 10 people—or 592 million individuals worldwide—will have diabetes by the year 2035. Uncontrolled blood glucose is a major risk factor for diabetes-related long-term micro- and macrovascular complications including retinopathy, neuropathy, nephropathy, and cardiovascular disease (CVD). These complications are associated with significant economic, social, and personal costs, making diabetes one of the most prominent health challenges (110).

T2DM: type 2 diabetes mellitus

CVD: cardiovascular disease

FBG: fasting blood glucose

PPG: postprandial plasma glucose

Poor glycemic control has a well-established role in the pathogenesis of diabetes-related complications and is a primary therapeutic target for diabetes management (6). Guidelines from the American Diabetes Association indicate that in normoglycemic individuals, glycemia is maintained within a narrow range [fasting blood glucose (FBG) < 5.6 mmol/L], particularly during the postprandial state [postprandial plasma glucose (PPG) < 7.8 mmol/L] (6, 146, 226). Conversely, dysregulation of glycemia in diabetes encompasses both chronic hyperglycemia and acute glucose fluctuations over time. It has been shown blood glucose concentrations fluctuate to a greater extent

in individuals with diabetes compared to healthy controls (18). These variations are not limited to PPG excursions. A primary goal of diabetes management, therefore, is to reduce diabetes complication risk by maintaining blood glucose levels close to the physiological range without risking hypoglycemia and by minimizing blood glucose variability.

Current clinical practice for assessing and monitoring glycemic control for diabetes management is centered on glycated hemoglobin (HbA1c). HbA1c is considered the gold standard for assessing blood glucose control and has a well-established association with diabetes complication risk (6, 111, 112). However, HbA1c alone does not entirely explain the onset and progression of diabetes complications. HbA1c provides limited characterization of glycemic variability (GV; a measure of the degree of blood glucose changes over time), which is recognized to contribute to diabetes-related complications (145). This has raised consideration for the use and assessment of GV in clinical diabetes management and interest in therapeutic approaches that target and modify GV.

This article reviews the concept of GV by examining techniques for GV assessment and quantification, the evidence for GV as a risk factor for diabetes complications, and the implications of GV as a marker of glycemic control for diabetes management. The influence of dietary factors on GV and nutritional considerations for GV management in T2DM are also discussed.

HbA1c: glycated hemoglobin

GV: glycemic variability

MARKERS OF GLYCEMIC CONTROL AND COMPLICATIONS IN DIABETES

HbA1c and fasting blood glucose are typically measured to assess glycemic control in current clinical practice for diabetes management.

Glycated Hemoglobin

HbA1c measures the degree to which hemoglobin A1c is bound by glucose in erythrocytes (33) and correlates strongly with the average of multiple glucose measurements taken throughout the day (188). Glucose levels in the preceding 30 and 90–120 days determine approximately 50% and 10% of HbA1c levels, respectively (217). HbA1c reflects long-term glucose control by identifying states of sustained hyperglycemia in the preceding 2–3 months, corresponding to the half-life of erythrocytes (34).

Data from several large-scale randomized controlled trials (RCTs) (1, 2, 72, 213, 222), including the Diabetes Control and Complications Trial (DCCT) and the UK Prospective Diabetes Study (UKPDS), show that lower HbA1c levels are associated with reduced diabetes complication risk. A meta-analysis of prospective cohort studies showed that pooled relative risk of CVD increased by 18% with every one absolute percentage point increase in HbA1c (195).

Over a median 10 years of follow-up, data from the UKPDS demonstrated a 21% risk reduction for diabetes-related deaths, 14% risk reduction for myocardial infarction, and 37% risk reduction for microvascular complications for every 1% absolute reduction in HbA1c in newly diagnosed T2DM patients (213). This study further demonstrated that although a median HbA1c of 7% achieved by intensively targeting normalization of FBG <6 mmol/L with pharmacotherapy produced a 25% greater reduction in microvascular complications compared to diet treatment, only a borderline significant reduction in myocardial infarction risk was evident ($p = 0.052$) (227). Similarly, the DCCT, a nine-year study of 1,441 type 1 diabetes (T1DM) participants, showed intensive insulin therapy involving three or more daily insulin injections or a continuous insulin infusion pump to maintain near-normal glycemia (HbA1c $\leq$ 6.05 mmol/L) reduced the risk of retinopathy, nephropathy, and neuropathy by 39–76% compared to conventional therapy

involving one to two insulin injections daily and standard diabetes education and counseling (222). Although HbA1c was identified as the primary risk determinant of the effects, accounting for 96% of this treatment effect (223), only 6.6% of the variation in retinopathy risk across the entire study cohort was explained by the treatment group alone (133), and only 11% of the difference in retinopathy risk was attributed to HbA1c and diabetes duration. Further observations showed that some patients developed microvascular complications despite achieving acceptable HbA1c levels. Collectively, these results suggest that HbA1c and FBG may not entirely account for diabetes-related vascular complication risk, including CVD, and other features of glycemia may contribute. Obesity—in particular visceral obesity—has been established as independent risk factor for the development of dyslipidemia, hypertension, CVD, nonalcoholic fatty liver disease, and other adverse cardiometabolic risk factors. These factors, occurring in synergy with the diabetic state, may also contribute to the development of diabetes-related vascular complications (231).

MBG: mean blood glucose

IGT: impaired glucose tolerance

In addition, hypoglycemic episodes, short-term glucose fluctuations, and transient hyperglycemia do not significantly alter HbA1c (33, 192). Epigenetic studies show that hyperglycemic spikes sufficient to cause persistent increases in proinflammatory gene expression are too transient to affect HbA1c (28, 74). Because HbA1c represents a time-averaged, mean level of glycemia, it fails to provide a measure of GV. Other studies show that HbA1c is poorly informative of the degree of PPG and is better correlated with preprandial glucose levels (21, 24). Consequently, isolated evaluation of HbA1c provides limited information on acute glucose excursions, and intra- and interday blood glucose fluctuations may present an incomplete assessment of diabetes management and glycemic control.

Fasting Blood Glucose

FBG provides a measure of an individual's ability to regulate blood glucose in the absence of dietary glucose input; FBG represents plasma glucose levels after an 8- to 12-hour fast (5). FBG is often used in clinical practice because it is economical, easy to use, and provides immediate information. A meta-analysis showed that an increase in FBG from 4.2 to 6.1 mmol/l was associated with a 33% increase in the relative risk of cardiovascular events (59). However, single, isolated blood glucose measurements inadequately describe a diurnal glucose profile and do not accurately reflect long-term glucose concentrations (21, 24, 188). For example, fasting hyperglycemia does not preclude the occurrence of hypoglycemia later in the day (225).

FBG only modestly correlates with indices of hyperglycemia and poorly predicts HbA1c and PPG (24, 25). FBG appears to contribute to overall hyperglycemia predominantly at higher HbA1c levels (>7.6%) (157, 185) but may progressively underestimate HbA1c and mean blood glucose (MBG) at higher glucose levels (188).

The DECODE (Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe) study highlights the limitations of the exclusive use of FBG to identify glucose intolerance. Data from 13 prospective European cohort studies with mean follow-up of 7.3 years showed the greatest number of excess deaths occurred in individuals with normal FBG (≤6.0 mmol/L) and impaired glucose tolerance (IGT; 2-hour post–75 g glucose challenge: 7.8–11.0 mmol/L) (23, 221). Further analysis showed that 2-hour post-load blood glucose, but not FBG, was associated with increased cardiovascular or all-cause mortality risk. Thus, diabetes management based solely on FBG would fail to identify individuals at increased risk of postprandial hyperglycemia–associated mortality.

Overall, these studies suggest that HbA1c and FBG may not provide a comprehensive reflection of glycemic exposure to end-organ tissues and highlight the relevance of considering other markers of glycemic control in diabetes management.

Postprandial Plasma Glucose

OHGAs: oral hypoglycemic agents

Another component of dysglycemia, PPG, has been implicated in independently contributing to the pathogenesis of diabetes complications and may address the limitations of established clinical measures of blood glucose control (30, 105). PPG contributes to individual GV and reflects blood glucose excursions within the four hours post food ingestion (109), which corresponds to the average time required for dietary carbohydrate digestion and absorption (70). PPG is typically measured 1–2 hours postmeal, which approximates the time to peak glucose in individuals with diabetes (4). Postprandial hyperglycemia and acute glucose excursions are frequently observed, even in individuals with satisfactory glycemic control and HbA1c levels (<7%) (21, 22, 47). PPG elevations indicate early abnormalities in glucose homeostasis associated with T2DM when HbA1c levels rise above 6.5% (154). Elevated PPG precedes progression to clinical diabetes and fasting hyperglycemia, and it is a corollary of the decline in β-cell function, insulin deficiency, consequent impaired suppression of hepatic glucose production, and decreased peripheral glucose uptake (179).

Recent evidence suggests that elevated PPG contributes to suboptimal glycemic control (4), has detrimental effects on CVD risk (51), and plays a significant role in the etiology of diabetes complications (238). A meta-analysis of prospective studies showed that elevated PPG levels (8.3–10.8 mmol/L) in healthy individuals without diabetes significantly increased CVD risk by 27% relative to individuals with low PPG levels (3.8–5.9 mmol/L) (135). Additionally, a substantial body of epidemiological (12, 14, 40, 59, 66, 71, 85, 101, 137, 149, 181, 211, 221, 224) and pathophysiological (53, 54, 166) studies provide further support that elevated PPG is an independent predictor and risk factor for CVD and all-cause mortality, increasing risk by 1.2- to 3.5-fold.

Acute hyperglycemia and PPG fluctuations adversely affect both macro- and microvasculature by altering the pathophysiological mechanisms related to diabetes complications. These include increasing retinal vascular reactivity, oxidative stress, carotid intima-media thickness, and endothelial dysfunction (53, 55, 58, 69, 75, 102, 118, 158), which are surrogate CVD risk markers that reflect early manifestation of atherosclerosis and coronary artery disease (96, 172). Furthermore, compared to HbA1c, PPG has been reported to be a stronger predictor of diabetic retinopathy progression (203). In individuals at risk of T2DM, post-challenge glycemic spikes (the maximal increase in blood glucose above fasting levels) are strongly associated with abnormal carotid intima-media thickness compared to HbA1c or FBG (220).

In T2DM patients with HbA1c <7.3%, PPG contributes more significantly (~70–80%) to overall diurnal hyperglycemia than does FBG (24, 157), which suggests that PPG may provide a better indicator of glycemic control in patients with moderately elevated blood glucose. However, few studies have measured the association between HbA1c and PPG, and available studies have produced inconsistent results (10, 66, 132, 210, 220). The premise for PPG being a significant contributor to overall hyperglycemia is supported by data from pharmacological studies demonstrating that basal-bolus insulin regimens or biphasic insulin treatments incorporating rapid-acting insulin to reduce PPG excursions are more effective at reducing HbA1c than is long-acting basal insulin targeting FBG (17, 93, 199). Insulin regimens that achieve better PPG control have also been associated with lower HbA1c (15); better myocardial and vascular function (189); reduced myocardial perfusion abnormalities in the postprandial diabetic state (194); improved endothelial function (45); delayed onset and progression of diabetes retinopathy, nephropathy, and neuropathy (173, 202); and reduced all-cause mortality in diabetes patients after acute myocardial infarction (141).

Similarly, oral hypoglycemic agents (OHGAs), including α-glucosidase inhibitors (8, 45, 57, 99), glucagon-like peptide 1 (GLP-1) derivatives (8), dipeptidyl peptidase- 4 (DPP-4) inhibitors (9, 13), glinides (76, 100, 189, 239), and short-acting sulfonylureas (39), that target PPG reduce

HbA1c and CVD risk markers (including carotid intima-media thickness) and systemic vascular inflammatory markers [C-reactive protein and interleukin (IL-6)] as well as the risk of myocardial infarction and other CVD events in patients with IGT and T2DM. An intervention trial utilizing an intensive treatment program incorporating diet, OHGAs, and insulin attributed the reduction in HbA1c primarily to decreases in PPG, which accounted for almost twice that of FBG changes (233). Additionally, 94% of patients who achieved the PPG target of <7.8 mmol/L achieved an HbA1c <7%, compared to only 64% of those who achieved the FBG target of <5.5 mmol/L. Results from these pharmacological studies suggest that HbA1c may lack sensitivity to monitor treatment efficacy, and targeting PPG excursions may be critical for achieving HbA1c objectives and optimizing glycemic control to minimize complication risk (43).

Despite this suggestion, recent clinical trials examining whether improved PPG control reduces CVD risk have not consistently shown additional benefit; however, that may in part be a study design artifact. The HEART2D (Hyperglycemia and Its Effect After Acute Myocardial Infarction on Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus) study compared insulin strategies targeting PPG or FBG in 1,115 individuals with T2DM (184). Although the prandial-targeted group achieved a lower daily mean PPG (7.8 versus 8.6 mmol/L) and 2-hour PPG excursion (0.1 versus 1.3 mmol/), HbA1c was similar between groups (7.7% versus 7.8%) with no difference in primary CVD event risk. However, because fewer than expected CVD events occurred, this trial was ended prematurely after 2.7 years, which could have prevented any differential effects between the treatment targets from being realized over a longer period.

Although CVD is a primary cause of mortality in diabetes, macrovascular complications appear to be less directly influenced by hyperglycemia or intensity of diabetes control compared with microvascular complications. Advanced T2DM patients with either known CVD or multiple CVD risk factors in other trials, such as ACCORD (Action to Control Cardiovascular Risk in Diabetes), ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation), and VADT (Veterans Affairs Diabetes Trial), that targeted HbA1c (<6%) with intensive therapy also demonstrated no benefit of intense glycemic control for reducing CVD events or mortality (1, 2, 72). This suggests that nonglycemic-related risk factors in T2DM such as hypertension, hyperlipidemia, and obesity also play a significant role in CVD risk. For example, the HEART2D study examined a T2DM population at high risk of CVD who concomitantly took a significant number of medications. It is therefore possible that this trial was underpowered to detect any differences between groups in CVD outcomes following PPG control due to confounding influences of other cardiometabolic factors (42, 44). In addition, although a statistically significant PPG difference of 0.8 mmol/L was achieved between treatments, the a priori target of 2.5 mmol/L was not reached. The UKPDS and DCCT/EDIC (Epidemiology of Diabetes Interventions and Complications) studies showed that the macrovascular complication–reducing effects of intensive glucose therapy were only realized after 10–17 years of posttrial monitoring (106, 167). This raises the possibility that the small PPG difference achieved was insufficient to influence cardiovascular outcomes, particularly over a short duration. Moreover, it is plausible that hyperglycemia control may have differential effects on primary and secondary CVD prevention in T2DM. Hyperglycemia treatment in T2DM may need to occur early to prevent CVD progression, and commencing intensive glucose control and treating PPG after CVD is established may be less effective (11, 42, 44). However, a subgroup analysis of the HEART2D study showed that older patients (>65 years) who received PPG treatment compared to the FBG-targeted treatment experienced fewer CVD events and had significantly longer time to first CVD event [56/189 (29.6%) versus 85/210 (40.5%)] despite similar HbA1c levels (hazard ratio 0.69; 95% CI 0.49–0.96; $p = 0.029$) (183). This suggests that targeting PPG with insulin in older T2DM patients may be associated with a reduced CVD risk.

Studies that are better designed, longer term, and that utilize therapies that are more effective in targeting PPG are also required to establish the effect of modifying PPG on future cardiovascular events. In the NAVIGATOR (Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research) study of 9,306 people with IGT and established CVD or cardiovascular risk factors, allocation to nateglinide, a short-acting insulin secretagogue, compared with placebo for a median duration of five years did not significantly reduce the incidence of diabetes (36% versus 34%; hazard ratio 1.07; 95% CI 1.00–1.15; $p = 0.05$), core composite cardiovascular outcomes such as myocardial infarction or stroke (7.9% versus 8.3%; hazard ratio 0.94; 95% CI 0.82–1.09; $p = 0.43$), or extended composite cardiovascular outcomes (14.2% versus 15.2%; hazard ratio 0.93; 95% CI 0.83–1.03; $p = 0.16$) (168). However, it is important to acknowledge that nateglinide treatment did not improve PPG, and higher 2-hour post–oral glucose tolerance test glucose levels were observed. Different insulin secretagogues vary in their PPG-lowering efficacies, although the apparent lack of any observed effect could be partly attributed to withholding medication before oral glucose tolerance testing.

SMBG: self-monitored blood glucose

Overall, growing evidence supports the role of PPG as an independent risk factor for the development of diabetes complications. This evidence forms the basis of the International Diabetes Federation guidelines, which emphasize the importance of PPG control by medical or dietary interventions as part of an overall strategy to improve glycemic control (46).

GLYCEMIC VARIABILITY

In addition to PPG, HbA1c, and FBG, GV is an emerging target for diabetes management. GV, defined by the amplitude, frequency, and duration of glycemic fluctuations around MBG, encompasses both diurnal hyperglycemic peaks and hypoglycemic troughs. Growing evidence suggests that wide oscillating glucose levels reflecting increased GV may be an independent risk factor for diabetes complications including CVD (36, 69, 120, 158, 165). Support for GV as a contributor to diabetes-related complication risk beyond PPG response is provided by studies that show hyperglycemia-induced endothelial dysfunction is greater when initial basal blood glucose levels are lower and the ensuing oscillation responses are larger (49). Reductions in hyperglycemic excursions that lower GV also reduce oxidative stress markers (41). These data suggest that oscillating glucose levels that produce damaging effects on endothelial function and oxidative stress may be more deleterious for the cardiovascular system than is chronic sustained hyperglycemia (50, 158).

GV does not alter HbA1c (67, 147, 199). Individuals with relatively stable diabetes may have HbA1c that is identical to those with labile diabetes, yet the latter group of patients experience far wider disparities in GV and marked differences in the frequency and magnitude of glucose fluctuations within their diurnal blood glucose profiles (129, 145). GV may therefore represent an important aspect of glycemia that is not reflected by conventional measures of glucose control, such as HbA1c and FBG.

Measurement of Glycemic Variability

The assessment of GV requires an evaluation of a patient's blood glucose profile attained from multiple readings sampled over time (196). The traditional self-monitored blood glucose (SMBG) approach requires the patient to collect sufficient capillary blood glucose samples to obtain an adequate representation of a typical diurnal pattern. However, the invasiveness and inconvenience posed to patients may limit the frequency of these blood glucose measurements. Consequently, SMBG may only provide limited information that is based on sporadic blood glucose measurements and may miss hyperglycemic and hypoglycemic fluctuations of actual glucose trajectories (145).

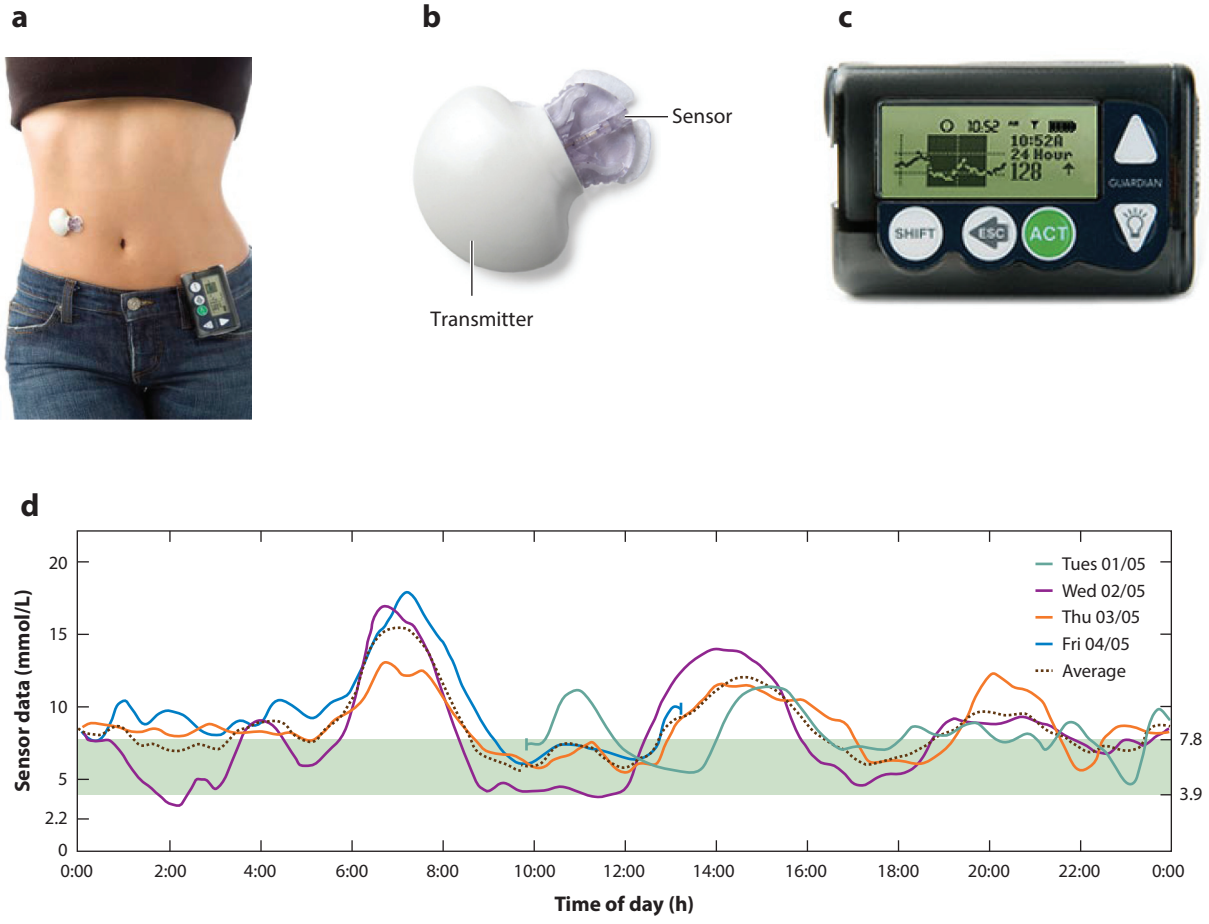

Figure 1

Illustration of a continuous glucose monitoring system (CGMS) device. (*a*) The typical components of a CGMS. The sensor measures subcutaneous interstitial glucose levels every five minutes and is commonly inserted into the abdominal area. (*b*) The transmitter attached to the sensor sends glucose data wirelessly to the monitor/receiver. (*c*) The monitor/receiver shows real-time glucose trends, with glucose readings displayed continuously. Figure reprinted with permission from Medtronic Australasia Pty. Ltd., NSW, Australia. (*d*) An example of daily glucose time trajectories for an individual who wore the CGMS device for four days.

CGMS: continuous glucose monitoring systems

Novel technological advancements have led to the development of continuous glucose monitoring systems (CGMS), which are holter-like sensor systems that continuously measure subcutaneous interstitial glucose levels at 5-minute intervals, 24 hours a day, 7 days a week (**Figure 1**). CGMS permit detailed diurnal glucose time series to be generated under free-living conditions. Information on the rate, direction, and magnitude of glucose excursions and oscillations can thus be visually examined and quantified mathematically through the computation of GV parameters. This greater precision of CGMS compared to SMBG provides the opportunity for a more definitive examination of the relationship between GV and clinical end points or diabetes complications. It also permits differentiation of the effects of a reduction in sustained chronic hyperglycemia from those of acute glucose fluctuations. CGMS may therefore offer advantages in measuring glycemic response (including GV) to evaluate and compare the efficacy of diabetes treatments for improving glycemic control.

Glycemic Variability Parameters

Given the suggested relevance of GV in the pathogenesis of diabetes complications, reductions in GV may represent an important target for T2DM management. Presently, in the absence of a uniformly accepted GV measure, several techniques have been developed to assess intraday and interday glucose fluctuations from CGMS data (121, 126, 128, 148, 152, 193, 197, 234). Most methods were originally developed for use with frequent SMBG but are now being applied to CGMS data. Although each metric has advantages and disadvantages, several GV metrics—including continuous overlapping net glycemic action (CONGA), mean amplitude of glycemic excursions (MAGE), and standard deviation (SD)—are strongly correlated (24, 187) and therefore underpinned by common constructs. Moreover, GV parameters are weakly correlated with FBG, PPG, and MBG measurements, indicating that GV conveys distinct and additional information (24). In the absence of a gold standard GV biomarker, it is prudent to consider an array of GV indices to obtain a comprehensive assessment of different aspects of GV in order to understand the influence of GV on the development of diabetes complications. A summary of GV parameters frequently used in research and the different aspects of GV they characterize are described below and summarized in **Table 1**.

Standard Deviation of Blood Glucose

SD measures the amount of variation or dispersion from the average score and is commonly used as an indicator of GV. Although SD omits consideration of the number of glycemic swings (captured by CONGA and MAGE), it correlates strongly with these other GV measures (24, 187) and represents a key target parameter for optimizing diabetes management. A study examining the association of several GV indices and HbA1c showed that SD had the strongest influence on the relation between MBG and HbA1c (132). High SD was associated with higher HbA1c levels for a given MBG, and this effect was more evident at higher HbA1c and MBG levels. It should be acknowledged that although this outcome was confirmed only in T1DM patients, the authors suggested that the T2DM sample examined may have been too small and the degree of variability too low to realize any interaction.

Coefficient of Variation of Blood Glucose

The coefficient of variation (CV) of blood glucose represents the ratio of SD to MBG. By correcting for MBG, CV represents a normalized measure of dispersion, which describes the spread of blood glucose levels that is independent of its unit of measurement. Therefore, CV may be useful for GV comparisons between groups with different glucose tolerances. Similar to SD, CV includes minor glucose fluctuations in its calculations. However, although more recent studies have reported CV, unlike SD, there are limited data comparing CV with HbA1c or other more established markers of GV.

Mean Amplitude of Glycemic Excursions

The mean amplitude of glycemic excursions (MAGE) represents a marker of within-day GV that is frequently used in research and described as the gold standard of GV assessment (153). MAGE calculation involves computing the arithmetic mean of the differences between consecutive peaks and nadirs, with the direction of measurement determined by the first qualifying excursion. MAGE quantifies major swings in glycemia that are >1 SD of MBG but excludes minor deviations (200),

Table 1 Summary of glycemic variability (GV) measures

GV measure	Definition	Method of calculation	Advantages	Disadvantages
Standard deviation (SD)	SD of all glucose readings Measures the dispersion from mean blood glucose	$\sqrt{\frac{\sum(x_i-\bar{x})^2}{k-1}}$ x_i, glucose reading $\bar{x}$, mean glucose k, number of observations	Straightforward and easily calculated with classical statistical method Widely used Provides a measure of inter- or intraday GV depending on frequency of blood glucose measurements	Does not consider the number of glycemic swings
Coefficient of variation (CV)	Normalized measure of dispersion by correcting for mean blood glucose Describes the spread of blood glucose independent from its unit of measurement	$\frac{SD}{\bar{x}}$ $\bar{x}$, mean glucose	Useful for comparisons between groups with different glucose tolerance	Does not consider the number of glycemic swings
Mean amplitude of glycemic excursion (MAGE)	Average amplitude of glucose excursions (upstrokes and downstrokes) that are greater than 1 SD Reflects major glucose fluctuations >1 SD mean glucose Measure of intraday GV	$\frac{\sum^{\lambda}}{n}$ If $\lambda > v$ λ, magnitude of each blood glucose excursion from peak to nadir (or nadir to peak) n, number of valid observations v, 1 SD of mean glucose for a 24-hour period	Most extensively used in the literature Reflects both upward and downward glucose fluctuations	Relativism in arbitrary definition of "significant" peak/trough (>1 SD) Does not differentiate between the magnitude of glucose oscillations Excludes minor fluctuations <1 SD of mean glucose Dependent on sampling frequency
Continuous overall net glycemic action (CONGA-*n*)	SD of differences between each observed blood glucose reading and the reading recorded n hour(s) previously Measure of intraday GV Specifically developed for continuous glucose monitoring	$\sqrt{\frac{\sum_{t=t_1}^{tk^*}(D_t-\bar{D})^2}{k^*-1}}$ k^*, number of observations where there is an observation $n \times 60$ minutes ago $m = n \times 60$ $D_t = GR_t - GR_{t-m}$, difference between glucose readings at time t and $(t-n)$ hours ago GR_t, glucose reading at time t minutes after start of observations t_i, time in minutes after start of observations of ith observation $\bar{D} = \frac{\sum_{t=t_1}^{tk^*} D^t}{k^*}$	Adaptable for varying time intervals to provide measures of short- or long-term variability Able to capture smaller glycemic swings over shorter time intervals Does not require identification of arbitrarily defined glucose thresholds/rises/falls Not affected by nonnormal, asymmetrical glucose profiles	Requires software for calculation
Mean of daily differences (MODD)	Mean absolute difference between blood glucose readings measured at the same time on consecutive days Measure of interday GV	$\frac{\sum_{t=t_1}^{tk^*}\lvert GR_t-GR_{t-1440}\rvert}{k^*}$ k^*, number of observations where there is an observation 1,440 minutes (24 hours) ago $GR_t - GR_{t-1440}$ = difference between glucose readings at time t and 1,440 minutes (24 hours) ago	Reflects consistency and stability of day-to-day blood glucose patterns	Affected by different daily lifestyle patterns including variation in exercise, therapy, irregular mealtimes, and eating habits Requires software for calculation

and it may therefore produce different results from other GV indices such as SD that do not differentiate between the magnitude of each glucose oscillation. MAGE has been shown to be independent of MBG. Higher MAGE readings are associated with increased glycemic instability, which reflects more variable blood glucose levels (197). Since MAGE reflects both upward and downward glucose changes, it may provide a more comprehensive measure of GV than postprandial parameters such as postprandial incremental area under the curve (iAUC). However, MAGE is dependent on sampling frequency, does not reflect the total number of fluctuations, and may still yield a high result from a single major rise or fall in blood glucose level in the sampled period. Furthermore, the 1 SD difference used in the calculation appears arbitrary, and some ambiguity exists on determining the start and end of a peak or nadir (212).

Continuous Overlapping Net Glycemic Action

Continuous overlapping net glycemic action (CONGA) provides a measure of intraday GV with the advantage of being adaptable for varying time intervals to provide measures of short- and long-term variability (148). For example, CONGA-2 and CONGA-4 describe the SDs of the differences between any individual glucose reading and a reading recorded either 2 or 4 hours previously. CONGA-2 is particularly relevant for detecting rapid and small glycemic excursions and is useful for assessing the GV of patients with well-controlled diabetes (37). CONGA also appears to be a more objective marker of GV because it does not require the assignment of any arbitrary threshold, unlike MAGE.

Mean of Daily Blood Glucose Differences

Mean of daily blood glucose differences (MODD) refers to the mean of the absolute difference between paired blood glucose values in two consecutive 24-hour periods (152) and measures GV between days. MODD reflects the consistency and stability of day-to-day blood glucose patterns, although different daily lifestyle patterns including irregular mealtimes and eating habits may influence MODD (205).

Area Under the Curve

The 24-hour cumulative exposure to glucose levels can be calculated as area under the curve (AUC) using the trapezoidal rule, which provides an indicator of overall glycemia. This can be normalized for total wear time of the CGMS device ($AUC_{per\ min}$). Similarly, postprandial glucose response can be determined by the iAUC over four hours following the beginning of each meal. However, AUC may not be sensitive enough to detect actual glucose fluctuations. Any increase in the incidence of hypoglycemic troughs below preprandial values may offset the incremental area above preprandial values from hyperglycemic peaks, thus reducing overall AUC but not reflecting actual GV reductions.

Role of Glycemic Variability in Contributing to Diabetes Complications

To date, epidemiological studies examining the effects of GV and the development of diabetes complications have produced ambivalent conclusions. This is partly due to the lack of consensus on the most appropriate method of GV assessment, and until recently also due to the lack of acceptable measurement tools to provide sufficient monitoring of the duration and frequency of blood glucose required to measure GV accurately. There also remains a lack of agreement on

the optimum duration required for adequate GV assessment. Past studies have measured GV from rates of change in blood glucose levels over time frames varying from years to weeks and hours within the day. Furthermore, blood glucose levels representing differing metabolic control (FBG, PPG) have been used to quantify GV. In earlier studies, GV was represented by variation in FBG over years, whereas in later studies, GV reflected short-term diurnal variations in blood glucose levels including FBG but predominantly PPG values. This has impeded the ability to establish consensus within GV research. Prior to the development of CGM technology, the use of SMBG depended on blood sampling frequency, which may have affected the accuracy and validity of any GV indicators computed. CGMS has now provided the opportunity to determine GV with greater reliability, particularly during prandial periods. Different methods have also been used to analyze the same glycemic data to derive various GV parameters that measure different aspects of GV. Some GV metrics consider both the fall and rise in blood glucose (SD), whereas others do not capture sustained hyperglycemia. Other metrics (such as MAGE) consider major glucose fluctuations but exclude minor oscillations. Overall, in the absence of an acknowledged gold standard, different studies have used different GV indicators, making direct comparisons difficult. Despite these shortcomings, and collectively considering the GV indices, the current literature provides the following understanding of the role of GV in the development of diabetes complications.

A series of prospective cohort studies has examined the relationship between GV assessed by CV-FBG or standard deviation (FBG-SD) of FBG values. A study of 5,008 T2DM patients aged ≥30 years showed GV to be a strong predictor of all-cause and CVD mortality over five years (136). Similarly, the Verona Diabetes study showed GV strongly predicted incidence of cardiovascular and all-cause mortality in 566 elderly T2DM patients aged ≥75 years (162, 163) and 1,409 T2DM patients aged 56–74 years (164), followed for five and ten years, respectively. However, a separate study performed within the Verona framework showed that only mean FBG was associated with all-cause mortality in younger patients (<65 years), although GV independently predicted total mortality in older patients (≥65 years) (240). Average glycemia over time (HbA1c and mean FBG), but not GV, also independently predicted microvascular complications, including development and progression of retinopathy in 1,019 T2DM patients over four years (241). In contrast, a separate study of 130 T2DM patients after five-year follow-up demonstrated that GV predicted diabetic retinopathy onset, independent of HbA1c (92), which was confirmed in a Japanese study of 170 T2DM patients after 27- to 40-year follow-up (218). For these studies, the FBG values used to calculate GV were obtained either retrospectively from clinical records in the three years preceding the follow-up period (162–164, 240) or from quarterly or annual blood glucose measurements collected over the study duration (92, 136). Considering FBG exclusively also means the variability of nonfasting glucose levels is overlooked. It therefore remains uncertain whether the data collection and computation methods used to determine CV-FBG or FBG-SD adequately assessed GV. However, these studies suggest that variations in preprandial glucose levels, independent of HbA1c, may influence the development of diabetes complications and survival rates.

A retrospective analysis of the HEART2D data showed an insulin treatment strategy targeting PPG that lowered intraday GV [assessed by mean absolute glucose change (MAG), which is the summated change in glucose per unit time, computed from seven-point SMBG profiles] did not reduce CVD outcomes in T2DM patients (206). However, it is important to note that other conventional GV indices, including SD and MAGE, did not differ between groups, which could explain the lack of effect on risk outcomes. Moberg et al. (151) showed in T1DM patients that GV measured by SD from SMBG data at five specified time-points every two days over four weeks was associated with the presence of neuropathy. Similarly, another 11-year cohort study

in T1DM patients showed GV, assessed by SD from SMBG data over a four-week period, was an independent predictor of peripheral neuropathy prevalence but not of other microvascular complications such as retinopathy or nephropathy (26).

Discrepancies in the findings from previous studies regarding the association of GV with diabetes outcomes may be an artifact of the limited tools historically available to obtain acceptable, accurate, and valid GV measures. Earlier studies attempted to compute GV from SMBG data (67, 147), with information derived from a limited number of glucose measurements through infrequent sampling that may not reflect actual trends obtained with CGMS data. Regardless of measurement frequency, SMBG does not quantify GV with the same degree of detail conferred by CGM, which provides greater sensitivity in detecting larger PPG excursions (81). In a study of 161 children and adolescents with T1DM, PPG excursions were found to be two- to fourfold greater when measured by three days of simultaneous CGMS compared with daily eight-point glucose profiles (81). This suggests that discrete blood glucose measurements may not reflect actual PPG peaks and are unable to quantify the duration of glucose peaks. Therefore, CGMS likely provides a more robust measure of PPG and GV indices.

Although of limited value, independent analyses of DCCT showed the risk of development or progression of retinopathy, nephropathy, and neuropathy in T1DM patients after five-year follow-up was not related to GV assessed by SD and MAGE (119, 207). Similarly, no association between GV (assessed by MAGE and SD) and the development of retinopathy was found in DCCT patients followed-up for $\geq$4 years. In fact, the major risk was identified to be conveyed by MBG (198). However, HbA1c variability (SD of HbA1c measurements) predicted microvascular risk (120). This is consistent with other studies that show HbA1c variability is an independent predictor of nephropathy and CVD events in T1DM patients (144, 216, 228), suggesting that longer-term GV may be more crucial for the development of microvascular complications. Longer-term data from the EDIC study, which collected data four years post-DCCT, also showed that average HbA1c but not GV (assessed by SD and MAGE) predicted the development of microvascular complications (122). Furthermore, GV (assessed by SD) was not significantly related to CVD risk, but MBG was a better predictor of macrovascular complications than was HbA1c (121). Although the large sample size, randomized controlled design, and assessment of clinical endpoints were strengths of the DCCT study, this trial was not originally designed to assess GV effects. GV was computed from pre- and postprandial seven-point SMBG profiles over 24 hours, collected quarterly over 4–5 years of follow-up, and thus findings from this study should be interpreted with some caution. Based on CGMS data from T1DM patients that showed considerable GV irrespective of HbA1c levels (116, 192), quarterly seven-point capillary glucose data may have provided an insufficient assessment of complete glycemic trends that failed to accurately reflect GV.

Studies investigating the relationship between GV and macrovascular complications showed that elevated GV (MAGE) independently predicted the risk of one-year major adverse cardiac events in patients (with or without diabetes) after acute myocardial infarction, whereas HbA1c did not (215, 229). In 344 T2DM patients, GV (MAGE) was also associated with the presence and severity of coronary artery disease and, in fact, was a stronger predictor of coronary artery disease than was HbA1c (214). In studies that have investigated surrogate markers of macrovascular disease, a hyperglycemic clamp study of 22 T1DM patients showed that GV (MAGE computed from 72-hour CGMS data) was positively associated with central blood pressure changes, which are implicated in vascular disease development (94). Although MBG and HbA1c correlated with measures of arterial stiffness (assessed by aortic pulse wave velocity and augmentation index), none of the measures of glucose control (HbA1c, MBG, MAGE) correlated with changes in arterial stiffness. This suggests that both acute glucose excursions and chronic hyperglycemia contribute to vascular damage but may mediate macrovascular disease development differently.

Corroborating these findings, 75 individuals, including 22 newly diagnosed with T2DM, with elevated MBG but low GV (%CV computed from 48-hour CGMS data) had flow-mediated dilatation and carotid intima-media thickness similar to those with low MBG but high GV (36). Both MBG and GV (%CV) independently predicted flow-mediated dilatation, suggesting that elevated GV prior to T2DM diagnosis may precede established hyperglycemia and is associated with endothelial dysfunction.

Collectively considering the research available, a significant challenge resides in the ability to summarize and compare the multitude of indices classified as markers of GV. It is challenging to cluster the differing GV indices reported synonymously without due consideration of critical differences. This may in part have contributed to the conflicting findings surrounding the prognostic value of GV as a marker of glycemic control. Because different GV indicators assess distinct aspects of GV, it is possible that large changes in blood glucose levels detected by some and not other measures of GV can affect vascular function and peripheral tissues differently. Presently, in the absence of a commonly accepted definition for GV, an appropriate alternative approach is to consider a range of GV indicators that measure different aspects of glucose fluctuations.

Glycemic Variability: An Important Pathophysiological Mechanism Increasing Oxidative Stress in the Development of Diabetes Complications

A pathophysiological model concatenating GV with conventional markers of glycemic control has been postulated for the development of diabetes complications (153). This model postulates that acute hyperglycemia activates excessive glycation and the generation of oxidative stress. It is conceivable that GV plays a role in the pathogenesis of diabetes complications via increasing oxidative stress, endothelial dysfunction, and free radical production in pathways independent of the glycation of hemoglobin (52). Vascular damage may be mediated by hyperglycemia-induced superoxide reactive free radical overproduction by the mitochondrial electron-transport chain in the context of deficient endogenous antioxidant defenses. This activates other superoxide cascades, augmenting the initial deleterious effect of hyperglycemia. Four biochemical pathways associated with the development of diabetes complications involving enhanced polyol activity, increased formation of advanced glycation end products, activation of protein kinase C and nuclear factor kB, and increased hexosamine pathway flux have been identified (29). Pathophysiological studies describing the process by which glucose oscillations potentiate the harmful effects of stable hyperglycemia on endothelial cells, inflammatory cytokines, and free radical detoxification support this notion (77, 107, 178, 182); glucose oscillations are possibly mediated by the "metabolic memory" phenomenon (108). GV (MAGE) reduction by DPP-4 inhibitors correlated with reduction in oxidative stress (nitrotyrosine) and proinflammatory markers (IL-6) in T2DM patients (186). Furthermore, attenuation of GV with restoration of normoglycemia after pancreas transplantation in T2DM patients reduced previously elevated oxidative stress levels (82). Increased oxidative stress present in diabetes promotes lipid peroxidation and persistent platelet activation that is pivotal in the pathogenesis of neurodegeneration, atherothrombosis, and CVD (175). This is evinced by the presence of elevated F_2-isoprostanes concentrations, a marker of free radical production that occurs in concert with in vivo oxidative stress activation (63, 64, 68).

A study of 21 T2DM patients with poor glycemic control (mean HbA1c 9.6%) and treated by OHGAs or dietary management showed that 24-hour urinary 8-iso prostaglandin $F_{2\alpha}$ (8-isoPGF$_{2\alpha}$) excretion significantly correlated with GV assessed by MAGE ($r = 0.86$, $p < 0.001$) but not with measures of sustained chronic hyperglycemia (HbA1c, MBG, or FBG) (158). This correlation was stronger than that observed with PPG ($r = 0.55$, $p = 0.09$), suggesting that GV amplifies the effects of PPG spikes on oxidative stress. These results were consistent with another

study, which showed oscillating glucose levels administered by a euinsulinemic, hyperglycemic clamp increased endothelial dysfunction, plasma nitrotyrosine, and 24-hour urinary 8-iso$PGF_{2\alpha}$ above that induced by constant hyperglycemia in normal and T2DM individuals on diet control (mean HbA1c 7.7%) (50). Oxidative stress, determined by urinary 8-iso $PGF_{2\alpha}$ excretion rates, was also an independent predictor of increased left ventricular mass index, a surrogate marker of cardiovascular damage that was correlated with GV (CONGA-2) but not HbA1c or MBG (69).

Other studies have not confirmed these results (204, 208, 230). In a group of T1DM patients, higher levels of urinary 15(S)-8-iso$PGF_{2\alpha}$ were observed compared to healthy controls, but GV (MAGE, CONGA, and MODD) was not associated with oxidative stress levels (230). A crossover trial of 40 poorly controlled T2DM patients (mean HbA1c 7.9%) on a combination of two oral agents showed that both prandial and basal insulin reduced urinary 8-iso$PGF_{2\alpha}$ excretion equally, although no relationship with GV (SD, MAGE, and MODD) was observed (208). However, the prandial insulin approach was more effective at improving glycemic control, with a trend toward greater reductions in GV (−8–9% overall; $p \geq 0.1$), which suggests that the study may have been underpowered. Similarly, no relationship between GV (SD and MAGE) and 8-iso$PGF_{2\alpha}$ excretion was observed in 24 well-controlled T2DM patients (mean HbA1c 6.9%) on OHGAs (204). However, this cohort had relatively good glycemic control, which suggests that the relationship between GV and oxidative stress may be more apparent at higher HbA1c levels.

The relationship between GV and oxidative stress may exist only in non-insulin-treated T2DM patients, which would explain the conflicting findings between T1DM and T2DM patients (156, 204, 208). A study in T2DM patients treated with OHGAs showed that those with higher HbA1c and MAGE had greater oxidative stress (increased 24-hour 8-iso$PGF_{2\alpha}$ excretion rates), suggesting that both sustained chronic hyperglycemia and GV significantly activate oxidative stress (156). However, this relationship was not observed in T1DM or T2DM patients on insulin therapy. Although insulin-treated patients had higher GV (MAGE) compared to patients on OHGAs, 8-iso$PGF_{2\alpha}$ excretion was within the normal range, with levels approximately half those of non-insulin-treated patients. In a subgroup of 10 T2DM patients on OHGAs, urinary 8-iso$PGF_{2\alpha}$ excretion rates were significantly reduced by greater than 50% after insulin therapy for 10 months, despite MAGE and HbA1c remaining constant. These data provide support for an antioxidant and inhibitory effect of insulin on oxidative stress. Experimental and clinical studies provide further evidence for an anti-inflammatory effect of insulin (61, 62, 237). Corroborating these findings, another study in T1DM patients showed that insulin reduced oxidative stress (urinary 8-iso$PGF_{2\alpha}$), inflammation, and endothelial dysfunction during acute hyperglycemia maintained by a glucose clamp (48). However, this effect was considered weak because restoration of endothelial function and inflammation occurred after vitamin C was coadministered with insulin.

Methodological differences may also have contributed to the discrepancies in findings among studies examining the relationship between GV and oxidative stress. Enzyme immunoassay (EIA) and mass spectrometry (MS) are commonly used for isoprostane assays (60). Although EIA is more sensitive, cross-reactivity with other isoprostane isomers can occur, thereby affecting reliability (134). The alternative, MS, which is widely accepted as the gold standard, has a higher specificity, particularly if tandem MS is used. But extensive sample extraction and derivatization may increase contamination and artifact generation and lead to poor recoveries (60, 209). Comparisons of both assays have produced inconsistent results, as both appear to measure different compounds (16, 68, 180). Therefore, comparisons of F_2-isoprostane levels derived from these techniques may have limited validity. Future assay refinements with more specific antibodies for EIA and the measurement of individual isomers by MS will help in making both assays more comparable (180). Moreover, other factors may confound the interpretation of existing studies. Pharmacotherapy such as statins, angiotensin-converting enzyme inhibitors, and angiotensin II

receptor antagonists, which target other CVD comorbidities frequently observed with diabetes, may also mitigate oxidative stress resulting from glucose fluctuations.

Collectively, these studies suggest that although its prognostic significance has not been fully elucidated, GV may be an independent predictor of diabetes complications, mediated by increases in oxidative stress. Limited studies have considered GV assessment on the development of DM complications, and data regarding the role of GV on the incidence or progression of clinical end points (such as myocardial infarction, stroke, and retinopathy) remain scarce. Greater evidence is required to confirm the contribution of GV to diabetes complications risk and to address the dearth of well-controlled prospective intervention studies on this topic.

Current evidence is derived largely from prospective observational, cross-sectional, or cohort studies that have mainly investigated surrogate markers of cardiovascular and diabetes complications (including flow-mediated dilatation, carotid intima-media thickness, and left ventricular mass). Many of the available RCTs, such as the UKPDS, VADT, ADVANCE, and ACCORD, that compare treatments of varying intensities on macrovascular outcomes in individuals with T2DM have limited assessment of glycemic control to HbA1c (1, 2, 72, 227). Further research using well-controlled RCTs targeting GV and PPG, over longer durations in varying patient populations, should be conducted to ascertain the benefits of tempering acute glucose fluctuations and PPG spikes and to determine whether surrogate markers of CVD risk or the development of diabetes complications are reduced. Current standards for diabetes care emphasize assiduous attention to managing comorbidities, such as hypertension and dyslipidemia, to influence the development of clinical endpoints and alleviate diabetes complication risk. Hence, it is important that these factors are considered in the design of future trials to ensure they are adequately powered to elucidate the effects of glucose fluctuations.

A greater understanding of the mechanisms underlying GV and effective strategies to negate its potentially adverse effects are also required. This underscores the importance of developing novel markers that comprehensively assess various aspects of glycemia (including GV) for blood glucose monitoring and devising effective therapies to improve these markers. Although some available pharmacologic agents that target postprandial hyperglycemia may concurrently mitigate GV, therapies presently in use should be evaluated for their effectiveness in improving GV beyond effects on HbA1c.

Role of Glycemic Variability in Hypoglycemia

Recent evidence suggests GV (assessed predominantly by SD), particularly if accompanied by frequent hypoglycemic episodes, may adversely affect the prognosis of critically ill patients (52, 73, 130, 169, 232). Strict glucose control (HbA1c < 6%) achieved by intensive therapy in the ADVANCE, ACCORD, and VADT studies was associated with increased risk of hypoglycemia (1, 2, 72). The ACCORD study was halted prematurely due to an increased mortality risk in the intensive glycemic control group (20). The treatment group also experienced more severe hypoglycemia, although the association between hypoglycemia and increased mortality was stronger in the control group (goal HbA1c: 7–8%). Intensive treatment in the DCCT was also associated with a threefold increase in the risk of severe hypoglycemia (223). Secondary analysis of the DCCT data showed that HbA1c, MBG, and GV (as measured by SD) independently predicted risk of hypoglycemia in T1DM patients (123).

A pathophysiological explanation for the association between hypoglycemia and increased cardiac vulnerability may be the hypoglycemia-triggered activation of adrenergic glucose counterregulation and the resultant hemorheological and hemodynamic changes (84). Some evidence posits that increased oxidative stress secondary to excessive glucose fluctuation may contribute (158).

The deleterious effects of vacillating glucose levels may not be limited to postmeal spikes but may also include hypoglycemic variability, characterized by rapid declines in blood glucose following meals, or asymptomatic hypoglycemia during interprandial periods that may increase risk (155, 225). Furthermore, severe hypoglycemia can be preceded by blood glucose disruptions (127), and GV has been proposed as a possible predictor of hypoglycemia, with studies showing that a lower GV is associated with fewer hypoglycemic episodes (131). This was demonstrated in a study of 222 T2DM patients in which a higher GV (SD) increased the risk of asymptomatic hypoglycemia (159), a risk negated when SD was <1.7 mmol/L regardless of MBG or treatment modality.

Lowering GV as a therapeutic target, independent of HbA1c, may therefore reduce oxidative stress and mitigate the burden of diabetic complications while also minimizing hypoglycemic risk. This supports the suggestion that comprehensive assessment of glycemic control throughout the day should extend beyond FBG and HbA1c to include GV to provide greater understanding of diurnal glucose patterns, particularly during postprandial periods. Thus, in intervention trials and in the clinical management of T2DM, targeting glucose excursions in addition to markers of mean glucose exposure (HbA1c or MBG) or FBG should be considered. Assessment of GV would allow the identification of aspects of hyper- and hypoglycemia (especially asymptomatic hypoglycemia during the interprandial or nocturnal period in patients on insulin or insulin secretagogues) not captured by traditional glucose control measures such as HbA1c. This offers the potential to examine whether interventions aimed at minimizing GV improve clinical outcomes, which would have high potential clinical significance for diabetes management and would inform target GV levels to minimize risk.

Normative Glycemic Variability Values for Normoglycemic Individuals and Individuals with Diabetes

In view of the emerging evidence for GV as an independent risk factor for diabetes complications, future studies should examine and establish target GV levels that assist in minimizing risk. In Caucasian adults, based on CGMS data, GV (SD) was approximately three times higher in individuals with T2DM than in those with normal glucose tolerance (3.2 versus 1.0 mmol/L) (146). The higher GV observed in individuals with diabetes was also reflected by an approximately six-fold greater increase in MBG range (23 versus 150 mmol/L) and 30% higher normalized AUC (5.6 versus 8.5 mmol.h/L). Comparable to these data, a median SD of 1.0 mmol/L has been reported in an Asian normoglycemic population (226). Another study assessing GV in populations without diabetes from varying ethnic backgrounds observed an SD of 1.5 mmol/L, CONGA of 4.6 mmol/L, MAGE of 1.4 mmol/L and MODD of 0.8 mmol/L (241). These data provide useful benchmarks to assess changes in GV markers resulting from therapeutic interventions aimed at reducing GV, which is important when considering GV in clinical diabetes management.

NUTRITIONAL MANAGEMENT OF GLYCEMIC VARIABILITY

The information above presents increasing evidence that GV plays an important role in the development and progression of diabetes-related complications and may represent a key therapeutic target. T2DM is intrinsically linked with lifestyle factors including obesity and other dietary factors amenable to nutrition therapy. GV may therefore be influenced by energy restriction for weight loss and dietary factors that can assist in optimizing glycemic control. Studies have shown that obesity and in particular excess visceral fat are associated with decreased peripheral insulin sensitivity and function (90). Given that elevated GV (particularly when present concomitantly with acceptable FBG control) may indicate insulin deficiency (104), it is possible that diet-induced

weight loss and reductions in adiposity that are well recognized to improve insulin sensitivity (125) may promote corresponding reductions in GV. This hypothesis is supported by preliminary data from our laboratory that showed a direct correlation between the change in several GV metrics (MAGE, SD, CONGA) and weight loss in response to a six-month weight loss intervention in adults with obesity and T2DM ($r = 0.38–0.47$, $p < 0.001$; J. Tay, C.H. Thompson, and G.D. Brinkworth, unpublished data). However, there is a lack of studies examining the effects of obesity (including visceral obesity) on GV. Future research will help to establish the effects of energy restriction, weight loss, and body fat distribution on GV.

GI: glycemic index
GL: glycemic load
LC: low carbohydrate
HC: high carbohydrate

There is also limited knowledge of the effects of various dietary patterns and nutritional factors on GV. An overarching objective in prescribing a particular dietary strategy will be its effectiveness in achieving and maintaining glycemic goals. Elevated GV may also indicate poor matching of carbohydrate intake with insulin availability, irregular snacking, gastroparesis, delayed or missed administration of prandial insulin, inadequate matching of basal insulin, or need for insulin pump therapy (104). Despite the individual specific factors responsible in each case, the demonstrated influence of dietary factors on GV underscores the importance of considering nutritional and dietary factors, beyond energy restriction, in diabetes and GV management.

Carbohydrate Quality, Quantity, and Distribution

Total carbohydrate quantity ingested is well established as the greatest determinant of PPG (4), although carbohydrate quality also influences glycemia (7, 201). iAUC increases in a dose-response manner to dietary carbohydrate and varies with the glycemic index (GI) of food when carbohydrate load is held constant (27, 235). The GI ranks foods on the basis of the incremental blood glucose responses they produce for a given amount of carbohydrate compared with an equivalent quantity of carbohydrate in glucose or white bread (115). Integrating these factors, the glycemic load (GL; derived by multiplying the total amount of dietary carbohydrate in food by its GI) has been proposed as a measure of a diet's overall blood glucose–raising potential (236). It is therefore possible to reduce GL by reducing dietary GI and/or total carbohydrate intake to create a low-GL dietary profile, which may be useful for improving glycemic control and lowering GV in T2DM.

Restriction of carbohydrate intake suppresses PPG spikes and prevents both excessive postprandial hyperinsulinemia and the inception of reactive hypoglycemia that collectively minimize GV. A clinical study in T2DM showed restriction of carbohydrate (from 55% to 20% total energy) in an energy balance state reduced HbA1c by 2.2% (from 9.8% to 7.6%) (86). PPG was similarly reduced in IGT patients when a low-carbohydrate (LC) or low-GI diet was consumed (236). However, the influence of GI and varying dietary carbohydrate loads on GV remain poorly understood.

Several recent studies have used CGMS technology to examine the effects of varying dietary carbohydrate content on blood glucose profiles and GV. Mori et al. (161) showed that switching from a high-carbohydrate (HC) diet (14.1 g carbohydrate/100 ml) to an isocaloric LC (8 g carbohydrate/100 ml), high-monounsaturated-fatty acid (MUFA) liquid diet for three months narrowed the range of GV (SD, MAGE, and AUC by 24-hour CGM) in 10 tube-fed T2DM patients. The incidence of hypoglycemic episodes was also reduced, and patients spent significantly less time in the hyperglycemia range. Falls in MBG and HbA1c (7.6% to 6.5%) were also observed despite concurrent withdrawal of or reductions in insulin therapy. Similarly, in a five-day crossover study conducted in 14 tube-fed T2DM patients comparing an HC (55–60% carbohydrate) diet, an isoleucine-containing liquid diet (47% carbohydrate), and an LC, high-MUFA liquid diet (32% carbohydrate), the LC diet produced the greatest reductions in MBG and GV (SD, MAGE, and AUC by 24-hour CGM) (160). In this study, the LC diet was associated with a significantly

smaller proportion of time spent in hyperglycemia, but there was no significant difference between the three diets for time spent in hypoglycemia. In individuals with IGT or normal glucose tolerance (NGT), Kang et al. (117) showed that PPG increased directly with increasing carbohydrate composition at breakfast. PPG was assessed by iAUC, time spent reaching postprandial glucose spike, and postprandial glucose excursion, defined as the difference between preprandial and peak postprandial glucose levels. It was further observed that the IGT group experienced greater postprandial glucose spike, blood glucose range, SD, and postprandial glucose excursion after consuming a medium-carbohydrate meal (45–65% of total energy) compared to the NGT group following consumption of an HC (>65% carbohydrate) meal. The IGT group also had similar PPG and MGB after an LC meal (<45% of total energy as carbohydrate) compared to the NGT group following medium-carbohydrate or HC meals. However, both the IGT and NGT groups had similar PPG and MBG responses after an LC meal. These data suggest that increasing the proportion of carbohydrate in meals increases GV, and the consumption of an LC diet may help to normalize blood glucose fluctuations in individuals with IGT at higher risk of developing overt T2DM.

NGT: normal glucose tolerance

Studies conducted in individuals with diabetes comparing diets differing in carbohydrate levels further support the use of LC diets to achieve enhanced glycemic control. In a study of 16 women with gestational diabetes, AUC and PPG were higher after three days' consumption of a higher-complex-carbohydrate (60% carbohydrate) diet compared to an isocaloric LC (40% carbohydrate) diet, although both GV markers remained within treatment targets (103). A recent 24-week randomized trial of 115 individuals with T2DM also demonstrated that consumption of an energy-reduced LC diet (carbohydrate: 14% total energy, 57 g/day) produced greater reductions in diabetes medication requirements and GV (SD, MAGE, CONGA, and MODD) compared to an isocaloric, HC, low-fat diet (carbohydrate: 50% total energy, 205 g/day) (219). Greater reductions in $AUC_{per\ min}$, MBG, and HbA1c were also observed with the LC diet compared to the HC diet in individuals with elevated baseline levels ($AUC_{per\ min}$ >18 mmol/L, MBG >8.6 mmol/L, and HbA1c >7.8%). Moreover, compared to the HC diet, participants on the LC diet were less likely to spend time in the hyperglycemic range and more likely to spend time in the euglycemic range, suggesting overall improvements in glucose regulation. In some of these studies reviewed, differences in carbohydrate levels between comparison diets were relatively small, but overall this evidence suggests carbohydrate restriction may be an effective strategy for reducing GV. Longer-term studies are needed to confirm the sustainability of these glycemic improvements and whether further carbohydrate restrictions confer greater reductions in GV parameters, in addition to PPG. These studies should also examine the dose-response relationship between carbohydrate intake and GV.

In addition to modifications to carbohydrate amount, carbohydrate distribution may be another important nutritional consideration for altering diurnal blood glucose response and GV. In a randomized crossover study, Pearce et al. (176) examined 23 adults with poorly controlled T2DM (mean HbA1c 8.6%) and compared the effects of consuming an energy-balanced, moderate-carbohydrate (40% energy) diet with either an even carbohydrate distribution across three meals (70 g carbohydrate/meal) or carbohydrate loading (125 g) at breakfast, lunch, or dinner and assessed PPG (PPG peak, time spent >12 mmol/L, and glucose AUC) from three-day CGMS. This study showed that an even carbohydrate distribution did not optimize blood glucose control, whereas carbohydrate loading at lunch provided the most favorable PPG profile. Furthermore, carbohydrate amount and GL at each meal were only weakly related to PPG peak, accounting for 16–17% of the variance in PPG peak. Because insulin resistance causes impaired suppression of gluconeogenesis and excessive glucose production in T2DM (38, 150), repeated carbohydrate exposure may potentiate sustained increases in PPG. Larger studies of longer

durations are required to ascertain the applicability of carbohydrate distribution strategies for the management of GV and glycemic control in T2DM.

Carbohydrate quality was considered in 20 T2DM patients in a comparison of two diets matched for macronutrient and dietary fiber content but varying in GI (57 versus 83); iAUC was shown to be 30% lower after 24 days consumption of the low-GI diet compared to the high-GI diet (114). Other studies have also investigated the impact of varying GI on blood glucose response and GV using CGMS. Buscemi et al. (35) showed in 24 obese adults without diabetes that 48-hour GV (%CV) decreased after consumption of a low-GI diet but increased after a high-GI diet (GI 44 versus 54). This was despite comparable reductions in MBG with both diets, which were energy matched and had similar macronutrient composition and carbohydrate content (55–57% total energy, 218–230 g carbohydrates/day). Endothelial function was also inversely correlated with GV that improved following consumption of a low-GI diet. Brynes et al. (31) also reported that a low-GI diet (GI = 49) consumed for seven days by 11 free-living patients with T2DM reduced FBG, MBG, and 24-hour AUC. A separate crossover study in 17 men with increased cardiovascular risk compared four ad libitum diets varying in carbohydrate content and source (32). After 24 days, an LC, high-fat diet [36% carbohydrate (GI = 61), 47% fat, 16% MUFA] was associated with a lower PPG profile compared to three other HC diet variations (46–51% carbohydrate) that were low GI (GI = 48), high GI (GI = 68), or high sucrose (GI = 62). Moreover, comparison of the three HC diets demonstrated that the low-GI diet promoted the most favorable PPG profile. Fabricatore et al. (79) examined the ecologic validity of GI and GL in free-living obese individuals with T2DM and reported GI was an independent predictor of glycemia and GV (AUC, SD, MAGE, and percentage of readings in euglycemic or hyperglycemic range) measured by three-day CGMS. GI accounted for 10–18% of the variance in each GV parameter, independent of energy and carbohydrate intake levels. GL and carbohydrate intake were positively associated with SD and were significant independent predictors of MAGE after adjusting for energy intake. These results provide further support that carbohydrate quantity and quality independently influence GV.

Protein

Dietary protein and amino acids are also important modulators of glucose metabolism, with acute meal studies indicating that coingestion of protein foods blunts blood glucose response to ingested glucose by ~20–30% (87). Evidence suggests that the key mechanisms underlying the protein-attenuating effects on PPG and GV are mediated by an incretin response that delays gastric emptying and enhances insulin secretion through augmented glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 secretion as well as by direct stimulation of β-cells by absorbed amino acids (3, 97, 98, 191). In vitro data show that insulin secretion from isolated mouse pancreatic islets increases when incubated with serum from healthy volunteers collected after consumption of carbohydrate-equivalent meals of whey protein compared to after consumption of a white wheat bread control meal (17 versus 4 g protein, respectively) (191). Plasma amino acids, GIP, and GLP-1 were 1.2- to 2.8-fold higher after whey ingestion, but the stimulatory effect of whey on insulin secretion was inhibited by a GIP receptor antagonist (−56–59%). This suggests that whey exerts its insulinogenic effect by preferentially increasing particular amino acids and stimulating the release of incretin hormones. In contrast to a 10-g whey protein preload, a 10-g whey protein hydrolysate given 30 minutes before a standard pizza meal to 21 healthy adults did not lower iAUC compared to when no whey was given, although both whey preloads increased insulin equally (3). This supports the existence of insulin-independent glucose-lowering mechanisms that require stimulation from intact protein digestion. Pre-meal protein drinks containing 9 g whey or soy protein

(+/− isoleucine, leucine, lysine, threonine, and valine) consumed before a 50-g carbohydrate meal by 14 healthy volunteers also reduced iAUC (97). Positive correlations between early insulin response, plasma amino acids, GIP, and GLP-1 were observed, which suggests that the PPG-lowering effect of protein may be mediated by a rapid early insulin response. This may be particularly relevant for improving glycemic control in T2DM and IGT, where an impaired first-phase insulin secretion is a documented indication of β-cell dysfunction (80). GLP-1 responses were notably higher in the early postprandial phase after consumption of the whey premeal drink supplemented with amino acids, which suggests that the increased incretin secretion could be attributed to the added amino acids. These results are further demonstrated in 15 individuals with T2DM, in whom the consumption of 50 g whey protein before a high-GI breakfast reduced PPG by 28%, increased early insulin secretion by 96%, and augmented GLP-1 levels by greater than twofold (113).

The study by Fabricatore et al. (79) also showed that GV (MAGE) was inversely associated with protein intake, supporting the results of studies in T2DM that demonstrate that a preload or coingestion of whey protein with carbohydrate attenuates PPG by slowing gastric emptying and stimulating insulin and incretin hormone secretion (113, 139, 171). Compared to reference meals with equivalent protein (29–30 g) and carbohydrate (46–50 g) content but no whey protein, the addition of 28 g whey protein to a high-GI breakfast and lunch increased insulin by 31–57% and reduced postlunch AUC by 21% in 14 individuals with T2DM (83). This observed reduction in AUC was comparable to that achieved with pharmacotherapy such as nateglinide and sulfonylurea (95, 124). GIP responses were higher after whey ingestion, but no differences in GLP-1 were shown. Ma et al. (139) showed in eight individuals with well-controlled T2DM (mean HbA1c 6.5%) that iAUC was halved after a 55-g whey protein preload was consumed 30 minutes before a high-carbohydrate (59-g) meal and was reduced by 45% when whey was consumed during the meal compared to when no whey was provided. Gastric emptying was also slowest, and insulin, GIP, and GLP-1 levels were higher, after the whey preload. This suggests protein supplementation as a preload may be an effective strategy at reducing GV, although increasing the protein content of the meal may also confer equivalent and dose-dependent effects (3, 98, 177). This dose-response relation between whey protein intake and PPG was demonstrated in 12 healthy adults who consumed whey protein drinks varying in protein content (4.5 g, 9 g, or 18 g) but equivalent in carbohydrates (25 g) (98). Consumption of each additional gram of whey protein reduced iAUC by 3.8 ± 1.4 mmol/l. The improvements in PPG observed in these acute studies were consistent with a five-week randomized, calorie-controlled crossover study of 12 adults with T2DM (mean HbA1c 8.0%) in which consumption of a high-protein diet (30% protein, 40% carbohydrate) produced a 40% reduction in AUC and a 0.5% absolute greater reduction in HbA1c (−0.8 versus −0.3%) compared to an isocaloric conventional low-fat diet (15% protein, 55% carbohydrate) (89).

Although proteins (and individual amino acids) can stimulate increases in insulin and glucagon without raising blood glucose, different protein sources may modulate postprandial glucose metabolism differentially, varying the reduced PPG response (87). This can be attributed to differences in amino acid composition and bioavailability that alter protein digestion and absorption kinetics. Besides being a major insulin secretagogue, in comparison with other proteins whey protein has a high branched-chain amino acid content (170) and is digested and absorbed more rapidly (19), resulting in marked postprandial amino acid responses and rapid insulin release. This may explain the greater potency of whey compared to other proteins in reducing PPG.

The data presented highlight the impact of dietary protein on GV and PPG regulation. However, most current available evidence has been derived from small single-day or single-meal studies that investigated the acute metabolic responses of dietary protein after test meals. This limits the conclusions that can be drawn. Further studies with larger sample sizes are required to verify

the chronic effects of dietary protein on glycemic control, including GV. Additionally, if protein preloads are more efficacious in reducing PPG by promoting early insulin release and reducing ensuing glycemic excursions, future studies should also investigate the optimum duration for pre-meal ingestion and the metabolic effects of more frequent protein feeding. Nevertheless, given that protein confers the greatest satiety of all macronutrients (174), the insulinotropic characteristics of protein suggest a clinically relevant strategy for the use of higher-protein diets to improve glycemic regulation in T2DM by mitigating PPG and GV. Although protein is an efficient insulin secretagogue in T2DM even in the absence of carbohydrate (190), the coingestion of protein and carbohydrate may have synergistic effects on insulin response (88). Therefore, dietary patterns that are restricted in carbohydrate and higher in protein may have greater glucose-lowering effects that could be particularly beneficial for T2DM management.

Dietary Fiber

Dietary fiber (particularly soluble fiber) is another dietary factor that may influence GV. High-fiber, low-GI foods are recommended as a preferred carbohydrate source by the Diabetes and Nutrition study group of the European Association for the Study of Diabetes because of their ability to reduce PPG by delaying glucose absorption (142, 143). A six-week randomized crossover study of 13 people with T2DM showed that compared to a moderate-fiber diet (total 24 g, 8 g soluble), a high-fiber diet (total 50 g, 25 g soluble) rich in soluble fiber from natural foods reduced FBG and produced 10% greater reductions in 24-hour AUC (56). Both diets had the same energy and macronutrient content (carbohydrate: 55% energy), but the dietary GI characteristics were not reported, and although most foods in the high-fiber diet were of intermediate GI, some were of low GI. In another study of 18 adults with T2DM, individuals randomized to consumption of a high-fiber (51 g/day) diet for four weeks had significantly greater reductions in GV (%CV) and PPG compared to a low-fiber (15 g/day), high-MUFA diet (65). Although both diets were isocaloric and had similar carbohydrate compositions (high fiber: 51% energy; low fiber: 44% energy), compared to the low-fiber diet, the high-fiber diet had a lower GI (88 units versus 58 units) and GL (205 versus 155), making it difficult to attribute the differential GV responses to isolated differences in dietary fiber content. Similarly, in a randomized trial of 63 T1DM patients, a high-fiber, low-GI diet (fiber 39 g; GI 70 units) matched in energy and macronutrient composition (carbohydrate 53–54% energy) to a low-fiber diet (fiber 15 g; GI 90 units) produced greater reductions in the number of hypoglycemic events and resulted in improvements in MBG and PPG (91). A 2% reduction in HbA1c in the 83% of patients compliant with the high-fiber diet was also observed (cf. 5.8% increase in patients on the low-fiber diet). Despite the available evidence, the simultaneous combination of high-fiber and low-GI foods has made it difficult to isolate the observed effects of nutritional factors on glucose response. This has led the American Diabetes Association to report that current available evidence remains inconclusive to recommend fiber intake levels for people with diabetes beyond those recommended for the general population (78). Although previous study designs have made it difficult to distinguish the effects of individual nutrients, these studies demonstrate that a dietary pattern that is high in (soluble) fiber (total fiber: 39–50 g/day) and with low GI (<70 units) may work synergistically to improve PPG and GV. Future study designs that control for energy intakes and other potential nutrient confounders will further the understanding of the independent glycemic effects of GI and dietary fiber.

In addition to previous studies examining fiber-rich whole foods, fiber supplement trials provide further support that dietary fiber may improve PPG in T2DM (138, 140). In a group of 40 T2DM patients at risk of malnutrition, Magnoni et al. (140) demonstrated that postprandial glucose excursion and iAUC were significantly lower in the group supplemented with a high-MUFA,

high-fiber (10 g fiber) oral nutrition supplement consumed over 12 weeks, compared to a control group supplemented with an isocaloric, fiber-free standard oral nutrition supplement. However, the lower GI and carbohydrate content in the high-fiber supplement group (carbohydrate 35% energy versus 55% energy) may also have contributed to the improved PPG response. In another randomized crossover study of 15 people with T2DM, five weeks' supplementation with 15 g/day of arabinoxylan-rich soluble fiber from wheat in fortified foods produced significantly lower 2-hour PPG compared to a control diet (total fiber 49 g versus 34 g) matched in energy and carbohydrate (55% energy) content (138).

Collectively, these studies provide preliminary evidence that GV can be modified by altering carbohydrate quality (GI), quantity (GL), or distribution, as well as by altering protein and fiber intake and should be a consideration for optimizing blood glucose control. However, inferences from current studies need to be considered with some caution given that the majority of studies were uncontrolled, with small sample sizes and short intervention durations. Dietary modification is an integral component of diabetes management, and these findings highlight the importance of considering GV in assessing the impact of dietary approaches in T2DM. Further research examining appropriate dietary compositions and nutritional factors that minimize GV will provide the requisite clinical evidence to inform dietary guidelines for T2DM management.

CONCLUSION

HbA1c remains the standard measure of optimal glycemic control in current clinical practice, with a large body of evidence demonstrating its strong relationship with the development and progression of diabetes complications. However, HbA1c may not exhaustively represent all facets of dysglycemia in diabetes, nor is it adequately sensitive to comprehensively detect clinically meaningful effects of interventional strategies on diabetes management. GV is a component of dysglycemia that may contribute independently to the pathogenesis of chronic diabetes complications, but it remains an underappreciated risk factor in T2DM partly because of early challenges in accurately assessing GV and the myriad of measurement indicators. Further well-controlled RCTs are needed to establish GV as an independent risk factor for diabetes complications and to confirm whether lowering GV improves prognosis by reducing the incidence or progression of diabetes complications. The ability to undertake this research is facilitated by the availability and continued development of CGMS technology, which provides an objective and comprehensive glucose monitoring tool for measuring GV modifications arising from treatments that target GV. Nevertheless, based on the current available evidence, we suggest that a comprehensive management strategy for achieving optimum glycemic control and preventing diabetes complications should include both standard clinical assessments of glycemic control (HbA1c and FPG), with consideration of targeting GV and PPG to achieve a favorable blood glucose profile. Lifestyle therapies encompassing effective dietary interventions have the potential to accomplish this, and several nutritional strategies that favorably influence GV have been identified. These diet strategies should be considered as part of a comprehensive approach to diabetes management.

SUMMARY POINTS

1. Glycemic variability (GV) is a measure of the amplitude, frequency, and duration of glycemic fluctuations around mean blood glucose.

2. GV is an emerging independent risk factor for diabetes complications and a marker of glycemic control.
3. Continuous glucose monitoring systems enable capturing of detailed diurnal glucose time trajectories under free-living conditions, permitting information on the rate, direction, and magnitude of glucose excursions and oscillations to be visually examined and quantified mathematically through computation of GV parameters.
4. Several techniques can be used to quantify intraday and interday GV. Each GV parameter has advantages and disadvantages and measures different aspects of GV. In the absence of a gold standard GV biomarker, comprehensive GV assessment should consider the measurement of an array of GV parameters.
5. GV can be influenced by several nutritional factors, such as carbohydrate quality, quantity, and distribution, as well as by protein and fiber intake.

AUTHOR CONTRIBUTIONS

All authors drafted the manuscript, revised the manuscript for intellectual content, and reviewed and approved the final manuscript.

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The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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