Significance of Glycemic Variability in Diabetes Mellitus

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Abstract:
The goal of diabetes treatment is to maintain good glycemic control, prevent the development and progression of diabetic complications, and ensure the same quality of life and life expectancy as healthy people. Hemoglobin A1c (HbA1c) is used as an index of glycemic control, but strict glycemic control using HbA1c as an index may lead to severe hypoglycemia and cardiovascular death. Glycemic variability (GV), such as excessive hyperglycemia and hypoglycemia, is associated with diabetic vascular complications and has been recognized as an important index of glycemic control. Here, we reviewed the definition and evaluated the clinical usefulness of GV, and its relationship with diabetic complications and therapeutic strategies to reduce GV.

Key words: glycemic variability, time in range, continuous glucose monitoring, diabetic microvascular complications, diabetic macrovascular complications

Introduction
The purpose of diabetes treatment is to maintain good glycemic control from the early stage of diabetes and to prevent the onset and progression of diabetic microvascular complications and arteriosclerotic diseases (1). For this purpose, understanding the status of glycemic control in patients is necessary, and hemoglobin A1c (HbA1c) has been used as a golden standard index of glycemic control. HbA1c is the most commonly used method for evaluating blood glucose control in clinical treatment and is recognized as the key surrogate marker for the development of diabetic complications. In fact, previous studies have revealed that achieving good glycemic control is associated with a lower incidence and lower progression of diabetic microvascular complications, while HbA1c is used as an indicator of glycemic control (2, 3). Subsequently, however, it was reported that strict glycemic control using HbA1c as an index does not lead to the suppression of cardiovascular disease (CVD), but rather to severe hypoglycemia, weight gain, and potentially increased cardiovascular death (4-7).

Although HbA1c represents the mean blood glucose levels over the past 1-3 months, it does not necessarily represent glycemic fluctuations, such as excessive daily hyperglycemia or hypoglycemia (7-10). Self-monitoring of blood glucose (SMBG) has been used to evaluate the status of daily glycemic control; however, SMBG can only evaluate the blood glucose levels at the time of measurement and cannot sufficiently evaluate hypoglycemia and hyperglycemia. Continuous glucose monitoring (CGM) provides a more detailed assessment of daily glycemic control than SMBG because it continuously measures glucose concentrations in the subcutaneous interstitium fluid. With the advancement of CGM technology, CGM has recently been used more and more frequently in clinical practice.

Recently, it has been reported that high glycemic variability (GV) is associated with the development and progression of diabetic vascular complications, the exacerbation of hypoglycemic risk, and the deterioration of patient quality of life (QOL) (11-17). Moreover, GV is now recognized as an important index of glycemic control. This article outlines the significance of GV in diabetes mellitus.

1. Definition of GV
GV is usually defined by measuring fluctuations of glucose or other parameters related to glucose homeostasis within a given time interval (17, 18). There are two types of GV: (i) long-term GV assessed by HbA1c and long-term
fasting and postprandial blood glucose levels; and (ii) short-term GV based on the intraday and interday variability in blood glucose (18, 19). Typical GV indices are shown in Table 1.

**Long-term GV**

Long-term GV is a measure of GV after several weeks or months and is assessed by HbA1c or fasting and postprandial blood glucose levels (18, 19). The variation in HbA1c and blood glucose levels between visits is often calculated using the standard deviation (SD) or coefficient of variation (CV) (18, 19). Variations in HbA1c are reported to be correlated with the mean blood glucose and HbA1c levels (28), and some studies have investigated this using methods such as variation independent of the mean (VIM) to eliminate the influence of mean values (31, 32).

**Short-term GV**

Short-term GV is an index of within-day and between-day glycemic fluctuations. Recently, short-term GV is more often evaluated by CGM than by SMBG. The SD is a typical index of short-term GV. Although the SD is easy to calculate, it has the disadvantage that it is easily affected by the mean glucose level. The CV is calculated from the SD and mean blood glucose and is recommended as a GV index for the ambulatory glucose profile (AGP) because of its relative sensitivity to hypoglycemia and ease of calculation in comparison to the SD (27).

The mean amplitude of glycemic excursion (MAGE) is often used as another short-term GV index (21). The MAGE focuses on the range of blood glucose levels from nadir to peak and does not evaluate the time from nadir to peak (33). In addition, not all blood glucose fluctuation is evaluated because only blood glucose fluctuation exceeding 1 SD from the mean is evaluated (34). Other GV indices include the J-index, which is calculated from the mean blood glucose and SD (35); the low blood glucose index/high blood glucose index, which is designed to be sensitive to the frequency and severity of hypoglycemia with hypoglycemia (23, 24); and the average daily risk range, which is designed to predict both severe hypoglycemia and hypoglycemia (25). The mean of daily differences (MODD) is often used as a between-day GV index (26). The MODD is the absolute difference between two glucose values measured at the same time within a 24-h interval. MODD reflects between-day GV.

Table 1. Glycemic Variability Metrics.

| GV metrics | Definition and interpretation | Ref |
|------------|-------------------------------|-----|
| A. Long-term GV | | |
| a. SD | Variation from the mean of HbA1c and BG between sequential visits. | 18 |
| b. CV | Magnitude of variability relative to mean HbA1c and BG between sequential visits. | 18 |
| B. Short-term GV | | |
| a. SD | Variation from the mean blood glucose. SD is easy to calculate and is the most used index of within-day GV. SD is highly influenced by the mean blood glucose. SD reflects within-day GV. | 19 |
| b. CV | Magnitude of variability relative to mean blood glucose. CV is calculated by dividing the SD by mean blood glucose and multiplying by 100 to get a percentage. CV reflects within-day GV. | 20 |
| c. MAGE | Average of absolute differences between glucose peaks and nadirs (each difference need to be greater than 1 SD from the mean). MAGE reflects within-day GV. | 21 |
| d. CONGA | SD of differences between a current blood glucose reading and a reading taken hours earlier. CONGA reflects within-day temporal GV. | 22 |
| e. LBGI/HBGI | Calculated by performing a logarithmic transformation to balance the amplitude of hypoglycemic and hyperglycemic ranges. LBGI and HBGI are indices for specific prediction of hypo- and hyperglycemia. | 23, 24 |
| f. ADRR | Sum of the daily peak risks for hypo- and hyperglycemia. ADRR is a risk indicator for both future extreme hypoglycemia and hyperglycemia. | 25 |
| g. MODD | Mean of all valid absolute value differences between two glucose values measured at the same time within a 24-h interval. MODD reflects between-day GV. | 26 |
| h. IQR of AGP | The spread of glucose data at given timepoints over several sequential days. IQR of AGP reflects the presence of day-to-day synchrony in glucose measures at a given time. | 27 |
| C. Time in ranges | | |
| a. TIR | Percentage of time spent within the target glucose range during the measurement period. TIR is known to be appropriate and useful as clinical targets and outcome measurements that complement HbA1c. | 27 |

GV: glycemic variability, SD: standard deviation, HbA1c: hemoglobin A1c, BG: blood glucose, CV: coefficient of variation, MAGE: mean amplitude of glycemic excursion, CONGA: continuous overlapping net glycemic action, LBGI: low blood glucose index, HBGI: high blood glucose index, ADRR: average daily risk range, MODD: mean of daily differences, IQR: interquartile range, AGP: ambulatory glucose profile, TIR: time in range.
High GV leads to CVD through endothelial dysfunction. Increases the cardiac workload (56). Thus, it is assumed that increases adrenaline secretion, induces arrhythmias, and in addition, the sympathoadrenal response during hypoglycemia involves cellular adhesion molecule and platelets (54, 55). In addition, hyperglycemia and GV-induced oxidative stress decreases the function of the vascular endothelium (52). Furthermore, hyperglycemia not only induces oxidative stress but also leads to vascular endothelial dysfunction through increased oxidative stress.

Although vascular endothelial dysfunction is an important early indicator of atherosclerotic disease, oxidative stress is also a key player in vascular endothelial dysfunction. In basic experiments, ROS overproduction and increased apoptosis of endothelial cells occur when human umbilical vein endothelial cells are cultured at alternating high and normal glucose concentrations in comparison to when they are cultured at sustained high glucose concentrations (45). Oscillating glucose levels exacerbate oxidative stress and the vascular endothelial function more than constant high glucose levels, and hypoglycemia may be involved in the development and progression of diabetic microvascular complications through increased oxidative stress.

3. Relationship between GV and diabetic complications in clinical practice

Long-term GV

The relationship between long-term GV and diabetic microvascular and macrovascular complications in clinical practice is shown in Table 2. Variations in HbA1c and fasting plasma glucose levels are reported to be more associated with diabetic vascular complications than with HbA1c alone (28, 29). A meta-analysis reported that HbA1c variability is associated with diabetic microvascular and macrovascular complications and mortality in both type 1 diabetes mellitus (T1DM) and T2DM (77).

However, although long-term GV is correlated with the mean blood glucose and HbA1c, its relationship with short-term GV is unclear (78). Furthermore, because no studies have focused on the effects of long-term GV on ROS generation, further studies are needed.

Short-term GV

The relationship between short-term GV and diabetic complications in clinical practice is shown in Table 3. In cross-sectional studies involving patients with T2DM, short-term GV indices, such as SD and CV, and the TIR, which are assessed by CGM, are associated with diabetic retinopathy (DR), diabetic kidney disease, and diabetic peripheral neuropathy (DPN) (38-41, 68, 69). In addition, we reported that albuminuria and DPN were associated with the worsening of the TIR in Japanese patients with T2DM (42). For diabetic macrovascular complications, cohort studies have reported that short-term GV and the TIR, which are assessed by SMBG and CGM, are associated with CVD and cardiovascular death (71, 72, 74).

In contrast, analyses of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications for T1DM have reported that GV indices, such as SD and MAGE, which are assessed by SMBG, were not associated with DR or DPN (79, 80). Although the difference between SMBG and CGM may have affected the results (10, 81), a large-scale, prospective, long-term study is needed to clarify the relationship between short-term GV and diabetic complications.

4. Treatment strategies to minimize GV

Type 2 diabetes

For the treatment of patients with diabetes mellitus, setting therapeutic targets for each patient and managing blood glucose while avoiding excessive hyperglycemia, large glucose fluctuation, and hypoglycemia are important. Dietary and exercise therapies are useful for GV suppression (82, 83); however, drug therapy is also quite effective. Some studies on the effects of antidiabetic drugs on GV are
The Japanese Clinical Practice Guideline for Diabetes recommends patient-oriented use of antidiabetic drugs according to the condition of each patient (1). In Japan, dipeptidyl peptidase-4 inhibitors (DPP-4is) are frequently used (42). DPP-4is stimulate insulin secretion in a glucose-dependent manner and improve GV, but do not induce hypoglycemia when used as a single agent (97). In fact, DPP-4is improve GV without increasing the risk of hypoglycemia (84-87), and a cohort study has reported a reduction in CVD incidence (98). In addition, α-glucosidase inhibitors (α-GIs) can improve postprandial blood glucose levels and suppress CVD (99), and we have reported that the combination of DPP-4is and α-GIs can regulate the dynamics of glucagon-like peptide-1 (GLP-1) secretion dynamics and improve GV indices, such as SD and MAGE (100). In contrast, a meta-analysis investigating the association of DPP-4is, GLP-1 receptor agonists (GLP-1 RAs), and sodium-glucose cotransporter-2 inhibitors (SGLT-2is) with CV events showed that DPP-4is were not associated with lower CVD mortality, whereas SGLT-2is and GLP-1RAs were associated with lower CVD mortality (101).

Table 2. Association of Long-term Glycemic Variability Metrics and Diabetic Complications.

| Subjects       | N     | Design               | Main GV metrics | Main results                                                                 | Ref |
|---------------|-------|----------------------|----------------|-------------------------------------------------------------------------------|-----|
| Microvascular complications |        |                      |                |                                                                                |     |
| T1DM          | 1,441 | RCT                  | HbA1c-SD       | HbA1c-SD contributed to the development of DR and DN.                         | 28  |
| T2DM          |  821 | Prospective cohort   | HbA1c-SD       | HbA1c-SD was independently associated with the development of microalbuminuria. | 58  |
| T2DM          |  8,260| Prospective cohort   | HbA1c-SD       | HbA1c-SD affected (albuminuric) CKD.                                          | 59  |
| T1DM          |  2,019| Retrospective cohort | HbA1c-CV       | HbA1c-CV was associated with an increased cumulative incidence and risk of DR. | 60  |
| T1DM          |  35,891| Retrospective cohort | HbA1c-CV       | HbA1c-CV was independently associated with DR.                               | 61  |
| T2DM          |  32,481| Retrospective cohort | FG-CV, HbA1c-CV | FG-CV and HbA1c-CV predicted development of end-stage renal disease.         | 62  |
| T2DM          |  4,231 | Retrospective cohort | HbA1c-SD       | HbA1c-SD was associated with the development of DKD.                         | 63  |
| T2DM          |  36,152| Retrospective cohort | FG-SD          | FG-CV was significant predictors of diabetic polyneuropathy.                 | 64  |
| Macrovascular complications |        |                      |                |                                                                                |     |
| T2DM          |  4,399 | RCT                  | FG-SD, HbA1c-SD | HbA1c-SD and FG-SD were associated with combined macrovascular and microvascular events and macrovascular events. | 29  |
| Chinese without CVD |    | Prospective cohort   | FG-CV          | FG-CV increased the risk of CVD and all-cause mortality.                     | 65  |
| T2DM          |  1,791 | RCT                  | FG-CV, ARV     | FG-CV and FG-ARV were significantly associated with CVD.                     | 30  |
| T2DM          |  30,932| Retrospective cohort | FPG-CV         | FPG-CV was associated with PAD.                                              | 66  |
| T2DM          | 13,111-19,883| Retrospective cohort | HbA1c variability score | HbA1c variability was associated with increased risks of all-cause mortality, CV events, and diabetic microvascular complications. | 67  |
| Diabetes      | 624,237| Retrospective cohort | FPG-VIM        | As the quartile of FPG-VIM increased, the risk of stroke, MI, and all-cause mortality serially increased. | 31  |
| T2DM          |  9,483 | RCT                  | HbA1c-CV, VIM  | HbA1c variability indices were significantly associated with total mortality. | 32  |

GV: glycemic variability, T1DM: type 1 diabetes mellitus, RCT: randomized controlled trial. SD: standard deviation; DR: diabetic retinopathy; DN: diabetic nephropathy, T2DM: type 2 diabetes mellitus, CKD: Chronic kidney disease; CV: coefficient of variation, FG: fasting glucose, DKD: diabetic kidney disease, CVD: cardiovascular disease, ARV: average real variability, PAD: peripheral artery disease, VIM: variation independent of the mean, MI: myocardial infarction.
Table 3. Association of Short-term Glycemic Variability Metrics and Diabetic Complications.

| Subjects | N  | Design     | Main GV metrics | Main results                                              | Ref |
|----------|----|------------|-----------------|----------------------------------------------------------|-----|
| Microvascular complications |     |            |                 |                                                          |     |
| T2DM     | 3,262 | Cross-sectional | CGM-TIR         | CGM-TIR was associated with DR.                          | 38  |
| T2DM     | 982  | Cross-sectional | CGM-MAGE        | CGM-MAGE was a significant independent contributor to DPN.| 68  |
| T2DM     | 2,927 | Cross-sectional | CGM-SD          | CGM-SD was associated with DR.                           | 69  |
| T2DM     | 866  | Cross-sectional | CGM-TIR         | CGM-TIR was associated with albuminuria.                 | 39  |
| DM with DPN | 364 | Cross-sectional | CGM-TIR         | CGM-TIR was associated with painful diabetic neuropathy.  | 40  |
| T2DM     | 999  | Cross-sectional | CGM-SD, TIR     | CGM metrics were associated with the severity of DR or albuminuria. | 41  |
| T2DM     | 281  | Cross-sectional | CGM-TIR         | CGM-TIR was associated with albuminuria and DPN.          | 42  |
| T1DM     | 1,440 | RCT         | SMBG-TIR        | SMBG-TIR was associated with DR and albuminuria.         | 70  |
| Macrovascular complications |     |            |                 |                                                          |     |
| DM with stroke | 674 | Prospective cohort | SMBG-J-index | High GV was associated with 3-month cardiovascular composite outcome. | 71  |
| DM with ACS | 327 | Cohort study | SMBG-SD         | High GV was an independent predictive factor for midterm MACE. | 72  |
| T2DM     | 2,275 | Cross-sectional | CGM-TIR        | CGM-TIR was associated with CIMT.                        | 73  |
| T2DM     | 6,225 | Prospective cohort | CGM-TIR        | Lower TIR was associated with all cause and CVD mortality. | 74  |
| T2DM     | 445  | Cross-sectional | CGM-SD, MAGE, TIR | CGM-derived metrics were significantly associated with high arterial stiffness. | 75  |
| T2DM     | 853  | Cross-sectional | CGM-CV, TIR    | Higher CGM-CV and lower CGM-TIR were associated with higher cf-PWV. | 76  |

GV: glycemic variability, T2DM: type 2 diabetes mellitus, CGM: continuous glucose monitoring, TIR: time in range, DR: diabetic retinopathy, MAGE: mean amplitude of glycemic excursions, DPN: Diabetic peripheral neuropathy, SD: standard deviation, RCT: randomized controlled trial, SMBG: self-monitoring of blood glucose, ACS: acute coronary syndrome, MACE: major adverse cardiovascular events, CIMT: carotid intima-media thickness, CVD: cardiovascular disease, CV: coefficient of variation, cf-PWV: carotid-femoral pulse wave velocity

Table 4. Effects of Hyerglycemic Agents on Glucose Variability.

| Drug               | Comparator | Subjects | Main results | Ref |
|--------------------|------------|----------|--------------|-----|
| Teneligliptin      | Placebo    | T2DM     | Compared with placebo, Teneligliptin reduced TAR, CV, SD, and MAGE without increasing hypoglycemia. | 84  |
| Trelagliptin       | Alogliptin | T2DM     | Trelagliptin and alogliptin reduced SD and MAGE without inducing hypoglycemia. | 85  |
| Sitagliptin        | Glimepiride | T2DM    | MAGE decreased significantly in the sitagliptin group, but no significant difference was observed in the glimepiride group. | 86  |
| Vildagliptin       | Gliclazide | T2DM     | SG and MODD were significantly lower in the vildagliptin group than in the gliclazide group, but MAGE was not significantly different between the two groups. | 87  |
| Empagliflozin      | Placebo    | T2DM     | Empagliflozin improved postprandial blood glucose levels and increased TIR without increasing TBR. | 88  |
| Dapagliflozin      | Placebo    | T2DM     | Compared with placebo, dapagliflozin improved postprandial glucose, TIR, MAGE, and HBGI. | 89  |
| Canagliflozin      | Placebo    | T1DM     | Compared with placebo, canagliflozin improved daily mean glucose and SD assessed by SMBG, and increased TIR assessed by CGM. | 90  |
| Dapagliflozin      | Sitagliptin | T2DM    | Sitagliptin was superior to dapagliflozin in improving SD, MAGE and CONGA. | 91  |
| Degludec           | Glargine U-100 | T2DM | HbA1c was similar in both groups, degludec lowered episodes of severe hypoglycemia. | 92  |
| Degludec           | Glargine U-300 | T1DM | SD for degludec was non-inferior to that for glargine U-100 in terms of the incidence of CVD events. | 93  |
| Dulaglutide        | Glargine U-100 | T2DM | In combination with lispro, dulaglutide improved the proportion of CGM glucose values within the near-normoglycaemia range versus glargine U-100 without increasing TBR. | 94  |
| Ultra-rapid lispro | Lispro     | T1DM     | Mealtime URLi improved postprandial glucose compared to bedtime lispro. Postmeal URLi resulted in similar postprandial glucose control to bedtime lispro. | 95  |
| Faster aspart      | Aspart     | T1DM     | Faster aspart improved postprandial glucose and reduced TBR compared to aspart. | 96  |

TAR: time above range, CV: coefficient of variation, SD: standard deviation, MAGE: mean amplitude of glycemic excursions, SG: sensor glucose, MODD: mean of daily differences, TIR: time in range, TBR: time below range, HBGI: high blood glucose index, SMBG: self-monitoring of blood glucose, CGM: continuous glucose monitoring, T1DM: type 1 diabetes mellitus, CONGA: continuous overlapping net glycemic action, CVD: cardiovascular disease, URLi: ultra-rapid lispro
t2diabetic agents. Further studies are absolutely needed to investigate whether short-term GV improvement is directly associated with a reduced incidence of macrovascular complications.

As the duration of diabetes increases, the pancreatic β-cell function decreases and the proportion of patients on insulin increases (42). When starting insulin, it has been reported that starting with basal insulin was associated with less weight gain and hypoglycemia in comparison to starting with prandial bolus insulin or pre-mixed insulin (109). For basal insulin preparations, glargine U-300 and insulin degludec provide more stable basal insulin compensation than conventional basal insulin preparations, such as neutral protamine Hagedorn and glargine U-100 (110, 111). In fact, a meta-analysis has shown that glargine U-300 and insulin degludec reduced nocturnal hypoglycemia more than glargine U-100 (112-114).

GLP-1RAs improve GV by stimulating insulin secretion in a blood glucose-dependent manner and have a weight-loss effect by inhibiting gastric emptying and suppressing appetite (115). Oral GLP-1 RA, semaglutide, is also available now. In comparison to glargine U-100, dulaglutide increases the time in the normoglycemic range without increasing the TBR (91). Moreover, the combination of basal insulin and lixisenatide improved GV without increasing the risk of hypoglycemia (116). In addition, a meta-analysis has reported that the combination of basal insulin and GLP-1RAs was associated with a lower risk of hypoglycemia and improved glycemic control in comparison to multiple insulin injections (MDI) (117). GLP-1 reduces oxidative stress and inflammation and improves the vascular endothelial function (115, 118, 119). Furthermore, GLP-1RAs reduce the oxidative stress and vascular endothelial dysfunction induced by hyperglycemia and hypoglycemia, suggesting that GLP-1 RAs themselves have a vasoprotective effect (115, 120).

Type 1 diabetes

MDI is the basic therapy in T1DM with reduced endogenous insulin secretion. In Japan, SGLT-2is can be used in combination with insulin therapy for T1DM. The administration of SGLT-2is in patients with T1DM has been reported to significantly improve the TIR and GV without increasing the TBR (121). Alternatively, the concomitant use of SGLT-2is in patients with T1DM may increase the risk of diabetic ketoacidosis (122), and careful consideration should be given to indicated cases.

For basal insulin, insulin degludec and glargine U-300 provide more stable basal insulin compensation and are associated with a lower risk of nocturnal hypoglycemia in comparison to glargine U-100 in T1DM (112, 113, 123-125). Insulin lispro, insulin aspart, and insulin glulisine are used as bolus insulin. In addition, insulin preparations, such as ultra-rapid lispro (URLi) and faster aspart, which are added to conventional insulin lispro and insulin aspart to accelerate the rate of subcutaneous insulin absorption, can be used. In comparison to insulin lispro, URLi improves postprandial blood glucose levels and increases the daytime TIR, while decreasing nighttime the TBR (95). Moreover, faster aspart improves postprandial blood glucose levels more than insulin aspart, while reducing the TBR (96). In addition, it has been reported that continuous subcutaneous insulin infusion (CSIIT) therapy improves glycemic control and QOL while avoiding hypoglycemia, in comparison to frequent injection therapy (126).

The use of real-time CGM and flash glucose monitoring (FGM) reduces hypoglycemia and improves GV (127-129). Regardless of the method of insulin administration (e.g., MDI or CSII), the use of real-time CGM improves the TIR without increasing the TBR more than SMBG (130). Therefore, CGM may be considered for GV suppression in both T1DM and T2DM.

Conclusions

High GV is not only associated with diabetic complications but also may lead to hypoglycemia and a decreased QOL (11-17). In T1DM, the use of newer ultra-rapid-acting insulin preparations, such as URLi and faster aspart, improves GV (95, 96). In T2DM, the use of GLP-1RAs or SGLT-2is improves GV without increasing the risk of hypoglycemia (88-90, 117). Furthermore, GLP-1RAs and SGLT-2is have cardiovascular protective effects beyond GV (107, 108, 115). In both T1DM and T2DM, the use of real-time CGM or FGM improves GV, while avoiding hypoglycemia (126-128).

Various nonclinical and clinical studies have shown that high GV increases the risk of hyperglycemia, excessive blood glucose variability, and hypoglycemia, and subsequently induces oxidative stress, inflammation, platelet activation, and vascular endothelial dysfunction, which are associated with diabetic complications (44-55). In fact, long-term GV is associated with diabetic macrovascular complications (28-31, 65-67). However, reports on the relationship between long-term and short-term GV and oxidative stress are insufficient. Furthermore, there is no clear evidence of the association between short-term GV and diabetic vascular complications. Long-term prospective studies are needed to clarify the role of GV in the development and progression of diabetic complications.

The authors state that they have no Conflict of Interest (COI).

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