Original

Relationship between daily and visit-to-visit glycemic variability in patients with type 2 diabetes

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Abstract. The aim of the study was to explore the relationship between daily glycemic variability (GV) and visit-to-visit glycemic variability (VVV) in patients with type 2 diabetes (T2DM). A total of 156 outpatients with T2DM who had undergone continuous glucose monitoring (CGM) for 5 days were included in this study. Indices of GV, i.e., standard deviation and coefficient of variation (CV) of glucose, mean amplitude of glycemic excursion (MAGE) and mean of the daily differences (MODD) were calculated from the CGM data. VVV was calculated as CV of HbA1c or glycated albumin (GA) from HbA1c or GA measured for 3 years. Relationships among clinical parameters, GV and VVV were evaluated. Age was positively, and BMI and C-peptide index were inversely correlated with GV such as CV glucose and MAGE, while BMI was positively correlated with VVV. Mean glucose rather than GV was correlated with VVV. In contrast, time in range (TIR, 70–180 mg/dL) was correlated with both mean HbA1c or GA and VVV. In conclusion, GV and VVV were differently correlated with clinical parameters and were hardly correlated with each other. TIR was correlated with both mean HbA1c and VVV, suggesting that efforts to achieve optimal TIR are practical strategies to reduce VVV in patients with T2DM.

Key words: Daily glycemic variability, Visit-to-visit glycemic variability, Time in range

THE GOAL of treatment of patients with diabetes is to prevent the onset and progression of diabetic complications and achieve healthy longevity. To date, glycated hemoglobin (HbA1c), which is strongly related to the risk of onset and progression of diabetic complications, is the gold standard of glycemic control in patients with diabetes [1, 2]. In most of the current guidelines, glycemic control with HbA1c <7.0% is recommended to prevent diabetic complications [3].

However, since HbA1c reflects mean glucose level over one to two months, it is difficult to evaluate daily glycemic variability (GV) based on HbA1c level. An increase in GV has been shown to associate with increased reactive oxygen species (ROS) production and the presence of atherosclerotic cardiovascular disease (ASCVD) in patients with type 2 diabetes (T2DM) [4-6].

Furthermore, recent studies have reported that visit-to-visit glycemic variability (VVV) over months to years is also associated with the risk of development of diabetic complications as well as mortality in patients with T2DM independent of mean HbA1c [7-10]. Therefore, in addition to HbA1c, optimal control of GV and VVV may be important to prevent diabetic complications. However, to our knowledge, associations among GV, VVV and HbA1c are not fully characterized.

Therefore, in this study we aimed to characterize the relationship between GV assessed by continuous glucose monitoring (CGM) and VVV in Japanese patients with T2DM.

Methods

Subjects

We retrospectively reviewed a total of 232 Japanese patients with diabetes who sequentially underwent continuous glucose monitoring (CGM) in an outpatient setting between July 2012 and Feb 2016. After excluding cases with type 1 diabetes (T1DM) (N = 37), cases with steroid therapy (N = 8) and cases needing hospitalization for glycemic control or other reasons during the study period (N = 31), we enrolled 156 patients with T2DM (61 men and 95 women) in this study. Characteristics of the patients are shown in Table 1.

The study was approved by the Ethics Committee of Keio University School of Medicine. Since this was a retrospective study, written informed consent from each patient was waived.
Continuous glucose monitoring (CGM)

CGM was performed using iPro2 (Medtronic Japan Co., Ltd, Tokyo, Japan) for 5 days in an outpatient setting. During CGM measurement, patients were asked to conduct self-monitoring of blood glucose (SMBG) at least four times a day (pre-meal and bedtime), and the readings were recorded for calibration. The patients were blinded to the CGM readings during measurement.

After downloading the CGM data, indices of GV were evaluated as follows; mean glucose, standard deviation (SD) and coefficient of variation (CV) of glucose, mean amplitude of glycemic excursion (MAGE) and mean of the daily differences (MODD), as previously reported [11, 12]. In addition, time-in-range (TIR; percentage of time that the CGM readings were within the target range of 70–180 mg/dL), time-above-range (TAR; >180 mg/dL) and time-below-range (TBR; <70 mg/dL) were also assessed from the CGM data.

Visit-to-visit glycemic variability (VVV)

Information on each patient including HbA1c, glycated albumin (GA), plasma glucose and serum C-peptide immunoreactivity (CPR) levels was obtained from the medical records. HbA1c was measured by HPLC and expressed as NGSP value. GA and CPR were measured by enzymatic method and chemiluminescent enzyme immunoassay, respectively [11]. C-peptide index was calculated as serum CPR (ng/mL)/plasma glucose (mg/dL) × 100. Indices of VVV were evaluated as CV of HbA1c and GA, which were calculated from HbA1c and GA measured at outpatient visits for 3 years including the time of CGM. The number of measurements of HbA1c and GA was 13 ± 3 times.

Statistical analysis

The association between two variables was assessed with Spearman’s correlation coefficient and multiple regression analysis using the Statistical Package for the Social Sciences (SPSS, version 25.0, Chicago, IL, USA). Data are expressed as mean ± SD, and values of \( p < 0.05 \) were considered statistically significant.

Results

Association between glycemic variability and clinical parameters

The relationships between indices of GV/VVV and clinical parameters are shown in Table 2.

| Clinical parameter | Mean ± SD | \( p \) |
|--------------------|-----------|------|
| Age (years)        | 67 ± 11   |      |
| BMI                | 25.3 ± 7.3|      |
| Duration of diabetes (years) | 15.3 ± 9.5 |      |
| Plasma glucose (mg/dL) | 145 ± 40 |      |
| HbA1c (%)          | 7.0 ± 0.9 |      |
| GA (%)             | 18.3 ± 3.8 |      |
| Serum C-peptide (ng/mL) | 2.58 ± 2.4 |      |
| C-peptide index    | 1.79 ± 1.70|      |
| eGFR (mL/min)      | 66.0 ± 18.3|      |
| Hypertension (%)   | 57.7      |      |
| Dyslipidemia (%)   | 55.8      |      |
| Retinopathy (%)    | 23.7      |      |
| Nephropathy (%)    | 28.8      |      |
| Cardiovascular disease (%) | 9.0 |      |
| OHA (%)            | 79.5      |      |
| Insulin (%)        | 23.1      |      |
| GLP-1 agonist (%)  | 8.3       |      |
| Mean glucose (mg/dL) | 144 ± 33 |      |
| SD glucose (mg/dL) | 34.8 ± 13.3|     |
| CV glucose (%)     | 24.1 ± 7.3|      |
| MAGE (mg/dL)       | 45.0 ± 34.1|     |
| MODD (mg/dL)       | 31.0 ± 14.4|     |
| TIR (%)            | 80.0 ± 20.1|     |
| TAR (%)            | 18.5 ± 20.5|     |
| TBR (%)            | 1.5 ± 2.9 |      |
| Mean HbA1c (%)     | 7.1 ± 0.8 |      |
| SD HbA1c (%)       | 0.4 ± 0.3 |      |
| CV HbA1c (%)       | 6.1 ± 3.3 |      |
| Mean GA (%)        | 18.8 ± 3.3|      |
| SD GA (%)          | 1.5 ± 0.9 |      |
| CV GA (%)          | 7.6 ± 4.2 |      |

Plasma glucose and serum C-peptide were measured in a non-fasting condition. GA, glycated albumin; eGFR, estimated glomerular filtration rate; OHA, oral hypoglycemic agent; GLP-1, glucagon-like peptide 1; CGM, continuous glucose monitoring; SD, standard deviation; CV, coefficient of variance; MAGE, mean amplitude of glycemic excursion; MODD, mean of daily difference; TIR, time in range (70–180 mg/dL); TBR, time below range (<70 mg/dL); TAR, time above range (>180 mg/dL).

Table 1 Characteristics of subjects

| Characteristic          | Value (Mean ± SD) |
|-------------------------|-------------------|
| N (male/female)         | 156 (61/95)       |
| Age (years)             | 67 ± 11           |
| BMI                     | 25.3 ± 7.3        |
| Duration of diabetes (years) | 15.3 ± 9.5      |
| Plasma glucose (mg/dL)  | 145 ± 40          |
| HbA1c (%)               | 7.0 ± 0.9         |
| GA (%)                  | 18.3 ± 3.8        |
| Serum C-peptide (ng/mL) | 2.58 ± 2.4        |
| C-peptide index         | 1.79 ± 1.70       |
| eGFR (mL/min)           | 66.0 ± 18.3       |
| Hypertension (%)        | 57.7              |
| Dyslipidemia (%)        | 55.8              |
| Retinopathy (%)         | 23.7              |
| Nephropathy (%)         | 28.8              |
| Cardiovascular disease (%) | 9.0               |
| OHA (%)                 | 79.5              |
| Insulin (%)             | 23.1              |
| GLP-1 agonist (%)       | 8.3               |
| Mean glucose (mg/dL)    | 144 ± 33          |
| SD glucose (mg/dL)      | 34.8 ± 13.3       |
| CV glucose (%)          | 24.1 ± 7.3        |
| MAGE (mg/dL)            | 45.0 ± 34.1       |
| MODD (mg/dL)            | 31.0 ± 14.4       |
| TIR (%)                 | 80.0 ± 20.1       |
| TAR (%)                 | 18.5 ± 20.5       |
| TBR (%)                 | 1.5 ± 2.9         |
| Mean HbA1c (%)          | 7.1 ± 0.8         |
| SD HbA1c (%)            | 0.4 ± 0.3         |
| CV HbA1c (%)            | 6.1 ± 3.3         |
| Mean GA (%)             | 18.8 ± 3.3        |
| SD GA (%)               | 1.5 ± 0.9         |
| CV GA (%)               | 7.6 ± 4.2         |
also significantly correlated with CV of both HbA1c and GA. On the other hand, MODD was significantly correlated with CV of HbA1c or GA.

Plasma glucose and serum C-peptide were measured in a non-fasting condition. GA, glycated albumin; eGFR, estimated glomerular filtration rate; SD, standard deviation; CV, coefficient of variance; MAGE, mean amplitude of glycemic excursion; MODD, mean of daily difference; TIR, time in range (70–180 mg/dL); TBR, time below range (<70 mg/dL); TAR, time above range (>180 mg/dL). *p < 0.05. **p < 0.01.

### Table 2: Associations between glycemic variability and clinical parameters

| Mean glucose | SD glucose | CV glucose | MAGE | MODD | TIR | TAR | TBR |
|--------------|------------|------------|------|------|-----|-----|-----|
| Mean HbA1c   | SD HbA1c   | CV HbA1c   | Mean GA | SD GA | CV GA |
| Age          | 0.173*     | 0.225**    | 0.208** | 0.233** | 0.100 | -0.185* | 0.196* | 0.054 |
| Sex          | 0.106      | 0.173*     | 0.182* | 0.387** | 0.067 | -0.160* | 0.150 | 0.111 |
| BMI          | 0.059      | -0.172*    | -0.295** | -0.272** | 0.008 | 0.076 | -0.031 | -0.292** |
| C-peptide    | 0.013      | -0.162     | -0.253** | -0.180* | -0.213* | 0.102 | -0.048 | -0.252** |
| eGFR         | 0.030      | -0.044     | -0.106 | -0.123 | -0.004 | -0.069 | 0.034 | 0.001 |

| Mean HbA1c   | SD HbA1c   | CV HbA1c   | Mean GA | SD GA | CV GA |
|--------------|------------|------------|---------|------|-----|
| Mean glucose | 0.552**    | 0.422**    | 0.354** | 0.575** | 0.439** | 0.314** |
| SD glucose   | 0.412**    | 0.211**    | 0.121   | 0.582** | 0.321** | 0.164** |
| CV glucose   | 0.098      | -0.020     | -0.046  | 0.294** | 0.105   | -0.007 |
| MAGE         | 0.087      | 0.113      | 0.074   | 0.386** | 0.224** | 0.108 |
| MODD         | 0.373**    | 0.249**    | 0.186*  | 0.466** | 0.307** | 0.195* |
| TIR          | -0.477**   | -0.358**   | -0.310** | -0.592** | -0.408** | -0.275** |
| TAR          | 0.520**    | 0.396**    | 0.328** | 0.610** | 0.438** | 0.303** |
| TBR          | -0.148     | -0.184*    | -0.169* | -0.028 | -0.109 | -0.143 |

Association between GV and VVV

The relationships among indices of GV and VVV are shown in Table 3. Mean glucose was significantly correlated with CV HbA1c and GA (r = 0.354 and 0.314, respectively, both p < 0.01), while GV, such as CV of glucose and MAGE, was not correlated with either CV of HbA1c or GA. On the other hand, MODD was significantly correlated with CV of both HbA1c and GA (r = 0.186 and 0.195, respectively, both p < 0.05). TIR was also significantly correlated with CV of both HbA1c and GA (r = -0.310 and -0.275, respectively, both p < 0.01). The association between TIR and CV HbA1c or GA remained significant after adjustment for age, sex and BMI in the multiple regression analysis (β = -0.300 and -0.341, respectively, both p < 0.001).

Discussion

In this study, we characterized the relationships among GV, VVV and HbA1c in patients with T2DM. The main findings of the study were: 1) mean glucose rather than GV correlated with VVV, 2) older age and lower BMI and C-peptide index were associated with greater GV, while higher BMI was associated with greater VVV, and 3) TIR was inversely correlated with both mean HbA1c and VVV.

Although optimal control of VVV in addition to mean HbA1c may be important to prevent diabetic complications [7-10], factors affecting VVV are not well defined. Here we found that higher BMI was also associated with greater VVV. It is of note that, in contrast,
lower BMI was associated with greater GV, which might reflect lower beta cell function in individuals with lower BMI [11]. Older age was also associated with greater GV, consistent with our prior report [11], while there was no correlation between age and VVV. These findings suggest that different factors affect GV and VVV, respectively, and it is important to clarify the factors affecting VVV in order to achieve optimal glycemic control for prevention of diabetic complications. The causality of obesity in greater VVV remains uncertain because of the cross-sectional design of this study; however, weight loss should be emphasized not only to improve mean HbA1c level, but also, possibly, to improve VVV.

On the other hand, indices of GV were not correlated with VVV in this study, except that MODD, an index of day-to-day glycemic variability, was correlated with VVV, further suggesting distinct characteristics and/or regulatory mechanisms between GV, especially within-day GV, and VVV. An association of postprandial glycemic excursion, the main contributor to within-day GV, with the development of ASCVD has been reported [13-17]. Postprandial glycemic excursion and GV increase ROS production and promote endothelial dysfunction [18, 19]. However, the correlation between GV and the development of diabetic complications has been reported inconsistently in patients with diabetes [20, 21]. Moreover, interventions aiming to reduce postprandial glycemic excursion have failed to show improvement of CV outcomes [22-24]. The absence of a direct association between GV and VVV in this study also suggests that VVV is associated with ASCVD independently of GV, and reduction in VVV rather than GV could be more effective to prevent diabetic complications.

Finally, TIR, rather than GV indices such as CV glucose and MAGE, was associated with both mean HbA1c and VVV. TIR has been recently proposed as a glycemic indicator assessed by CGM [25]. It has been reported that TIR is associated with HbA1c level and the incidence of microvascular complications [25, 26]. Our results suggest that improvement of TIR results in improvement of not only HbA1c but also VVV. Thus, our findings support the use of TIR, in addition to HbA1c, as an important glycemic indicator in the management of patients with diabetes.

There are limitations of this study. Because of the retrospective study design, we were not able to assess the presence of other confounders such as patients’ adherence to treatment and seasonal changes in lifestyle which might affect VVV. Actually, the correlation coefficients between the parameters in this study were relatively small, i.e., 0.2–0.6, meaning coefficients of determination, \( R^2 \), of 4–36%. Also, because of the cross-sectional study design, it was not possible to assess the association between GV/VVV and the development of diabetic complications. GV was assessed by CGM for 5 days, rather than the currently recommended 14 days [25]. Since this study enrolled Japanese adults with T2DM, the results may not be applicable to those with T1DM or other ethnicities.

In conclusion, GV and VVV were differently correlated with clinical parameters and were hardly correlated with each other. TIR was correlated with both mean HbA1c and VVV, suggesting that efforts to achieve optimal TIR are practical strategies to reduce VVV in patients with T2DM.

Disclosure

None of the authors has any potential conflict of interest associated with this study.

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