

# Type 2 Diabetes and Glycemic Variability: Various Parameters in Clinical Practice

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## Abstract

It has become possible to measure blood glucose levels continuously from 24 h to approximately 2 weeks due to the recent development of relevant devices such as continuous glucose monitoring and flash glucose monitoring systems. This has enabled not only medical professionals but also patients to monitor details of glycemic variability (GV) which was not possible in the past. Details of GV for both short and intermediate periods can now be obtained, and it is important in patient care to appropriately evaluate the data obtained. Types of GV in terms of time frame vary from short-term to long-term. Several studies reported that long-term GV was related to micro- and macro-angiopathies in patients with type 2 diabetes mellitus (T2DM). However, there are still unknown aspects regarding the relationships of various durations of GV with prognosis. Further clinical trials are required to examine the mechanism of GV and to evaluate whether GV can be a valuable therapeutic target in treatment of patients with T2DM.

**Keywords:** Glycemic variability; Short-term glycemic variability; Mean of daily difference; Long-term glycemic variability; Visit-to-visit HbA1c variability; Continuous glucose monitoring; Type 2 diabetes mellitus

## Introduction

The importance of controlling blood glucose levels to prevent cardiovascular events in patients with type 2 diabetes is not a new concept [1, 2]. On the other hand, mortality rates were not decreased in recent clinical trials that set strict HbA1c control targets or, contrary to expectation, the mortality rate was reported to be higher in an intensive-therapy group than in a standard-therapy group [3-5]. One of the causes was attributed to hypoglycemia from short-term treatment intensification. It was also found that hypoglycemia can induce hyperglycemia associated with activation of sympathetic nerve

activity, namely, increasing glycemic variability (GV), and adversely affect the cardiovascular (CV) system [6]. Suppression of GV, primarily related to postprandial hyperglycemia, has been considered to be clinically important since postprandial hyperglycemia is involved in the onset of CV events [7, 8]. In recent years, however, because of the availability of a variety of anti-diabetes drugs, it is now easier to decrease blood glucose levels than previously. As a result, hypoglycemia is triggered more frequently; therefore, the importance of suppressing GV, including reactive hyperglycemia as mentioned above, is growing. However, the conventional method for evaluating GV required the collection of blood samples at each clinic visit, which was cumbersome. However, blood glucose levels can now be measured continuously from 24 h to approximately 2 weeks due to the recent development of relevant devices [9, 10]. This has enabled not only medical professionals but also patients to monitor details of GV that could not be monitored in the past. This development resulted in obtaining details of GV for both short and intermediate periods, and it is important to appropriately evaluate the data obtained. Meanwhile, many aspects of GV are still unknown, including the definitions of those parameters related to GV and their relationships with each other and with the patients' prognosis. We describe the current situations related to GV in this review.

## Glycemic Variability

GV can be evaluated according to various time frames such as short-term, intermediate-term, and long-term periods, although currently there is no clear definition of each. The oral glucose tolerance test (OGTT) that is used to diagnose diabetes can also evaluate the GV within a period of 2 h. This test could be considered to reveal short-term GV. However, in routine clinical practice, clinical data on GV are often reported according to the following: short-term GV, approximately 24 to 72 h (3 days) [11, 12]; intermediate-term GV, 3 days to 1 month, especially day-to-day variations [13-15]; and long-term GV, 1 month to several years, especially referring to HbA1c variations determined at routine clinic visits [16-18]. Furthermore, long-term GV includes seasonal variations [19-21]. Currently, there are few reports on long-term GV that is assessed for longer than 10 years. There is a wide range of indicators of GV based on various viewpoints even for short-term GV alone. In this article, we discuss indicators that are widely used in clinical practice and that have abundant sup-

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porting evidence.

### Short-Term Glycemic Variability

Since the continuous glucose monitoring (CGM) system [9] has been popularized, its versatility in daily clinical practice has increased remarkably. Representative usages for the results are the standard deviation (SD) and coefficient of variation (CV) based on mean blood glucose levels measured continuously for 24 h and the mean amplitude of glycemic excursions (MAGE), which reflects postprandial blood glucose [22, 23]. Among these, a number of reports related to factors such as oxidative stress and inflammatory markers have been made for MAGE [24, 25]. In recent years, drugs in various categories have been developed. Although previously it was difficult to clarify at which point within a 24-h time frame the effects of such drugs were exerted, this information has become clear with the advent of the CGM system. This system allows greater ease in determining the effects of existing drugs and the effect of additional administration of other anti-diabetes drugs [26, 27]. Furthermore, detection of hypoglycemia related to CV events has become possible [10, 28, 29]. Specifically, in patients with impaired awareness of the presence of hypoglycemia, the CGM system can determine the frequency of nocturnal hypoglycemia, which was impossible otherwise [30]. In addition, the relationship between the clinical state, such as an improvement in insulin resistance and GV, has been gradually elucidated, although results are only based on a short-term effect. We also reported the negative correlation between short-term GV evaluated in a 24-h period and baroreflex sensitivity (BRS), which is a sensitive measure of cardiovascular autonomic neuropathy [31]. Above all, the CGM system is considered to be particularly useful from the viewpoint of comprehension of dietary habits and GV among individual patients. Presumably short-term GV may change significantly depending on dietary and exercise amounts. Therefore, in daily clinical practice the CGM is suitable for assessment of variability in individual patients, but it may not be well suited for determining the association with long-term prognosis when considering issues of reproducibility and maintenance of continuity. Strictly speaking, CGM measures glucose levels in interstitial tissues; thus there may be a potential for discrepancies between CGM measurements and blood glucose levels [32, 33]. Moreover, this examination is invasive, even though mildly. There is also some room for improvement in terms of cost effectiveness.

### Intermediate-Term Glycemic Variability

Intermediate-term variability represented by day-to-day variability or the mean of daily difference (MODD) is difficult to evaluate, particularly in clinical practice. This is because, for example, people do not regularly ingest the same amount of food at the same time, especially those engaged in the modern life style. For that reason, there are few clinical reports on intermediate-term GV compared to short-term GV and long-

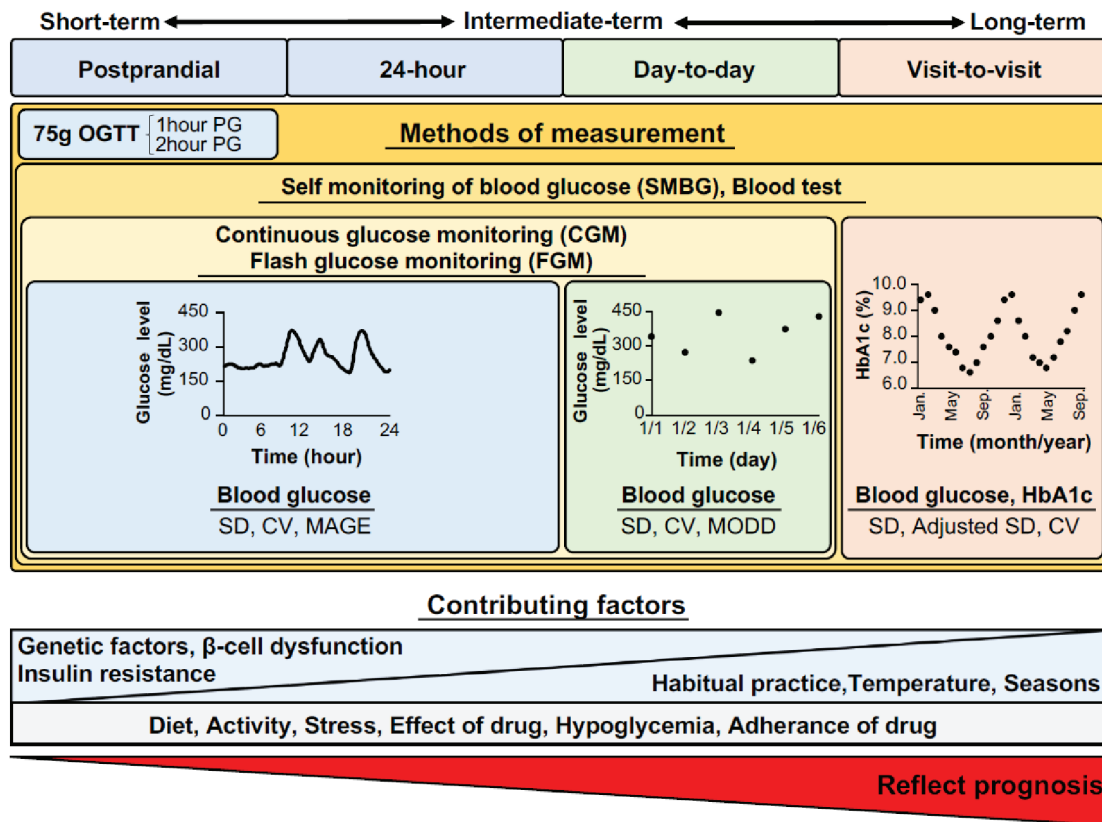
term GV. However, patients with irregular dietary habits may be likely to have a large intermediate-term GV. A report by Xu et al on diabetic microangiopathy noted that in patients with large day-to-day dietary variations there was an association with diabetic neuropathy [34]. Niskanen et al reported that patients with large day-to-day GV during fasting are at high risk for hypoglycemia [35]. Moreover, there has been a report on the relationship between improvement in the day-to-day GV and oxidative stresses [15], which may imply a relationship between the intermediate-term GV and macro-angiopathy. The results from these reports suggest that the day-to-day GV, i.e., intermediate-term GV, may correlate with long-term GV to some extent. In addition, we have also routinely observed intermediate-term GV caused by differences in the duration of drug actions due to differences in half-life and other factors. We also reported such differences in our clinical trials using insulin [36]. Intermediate-term GV is also useful in determining the effects of the duration of action of medications and other factors.

### Long-Term Glycemic Variability

Long-term GV is an index that has been frequently reported in recent years. This index can reflect changes in habits, with an orderly lifestyle reflected in slight GV. Long-term GV is often based on visit-to-visit GV in many cases. However, HbA1c in type 2 diabetic patients has often been shown to vary from season to season. In these reports, high values and low values are generally observed in winter and summer, respectively [19, 21, 37]. It has been reported that younger age, high body mass index, and amounts of dietary intake and exercise are involved in this seasonal phenomenon [16, 38]. Therefore, HbA1c evaluated on a visit-to-visit basis may be underestimated or overestimated depending on the timing of blood sampling. To evaluate the long-term GV more accurately, HbA1c should be assessed at the same time period and at the same frequency whenever possible. Moreover, it is desirable to compare HbA1c levels among patients whose clinical status matches to some extent, including the duration of disease.

In patients with large long-term GV, a variety of effects have been reported including involvement of micro-angiopathy such as an increase in CV events [17, 18, 39-42], onset of retinopathy [43], and onset of diabetic neuropathy [44]. Also noted have been vascular endothelial dysfunction [45] and healing time of foot ulcers [46]; development of chronic obstructive pulmonary disease (COPD) [47]; and development of Alzheimer's disease (AD) [48]. However, many of these were retrospective studies, and there are many uncertainties as to what conditions those patients had and which factors caused the increased long-term GV. A growing number of studies have reported that long-term GV was increased in the elderly and patients using insulin [49].

Few studies have directly compared short-term GV and long-term GV. However, in a sub-analysis in the Diabetes Control and Complications study of type 1 diabetic patients it was demonstrated that visit-to-visit HbA1c variability and average blood glucose levels had the largest impacts on the



**Figure 1.** Factors affecting the glycemic variability. OGTT: oral glucose tolerance test; PG: plasma glucose; SD: standard deviation; CV: coefficient of variation; MAGE: mean amplitude of glucose excursion; MODD: mean of daily difference.

HbA1c level, and daily blood sugar fluctuations (SD) also had some impact on HbA1c, but the effect was approximately 1/10 of the long-term HbA1c variation and 1/14 of the average blood glucose levels [50]. In addition, in our study, we investigated whether short-term GV evaluated by CGM or long-term GV evaluated by visit-to-visit HbA1c variability affected a decrease in BRS, which is also a marker of the onset of CV events. Results showed no significant difference, but there was a tendency for long-term GV to influence the decrease in BRS [51].

### Glycemic Variability and Prognosis of Type 2 Diabetes

Increased GV has already been considered to be a risk factor for the development of CV events. There are few prospective trials comparing groups with large GV and small GV due to ethical concerns. It was reported that short-term GV was related to prolongation of hospital stays and prognosis of patients [52]; however, such studies are scarce. This may be because it is unknown whether the variation measured during a particular time period is maintained thereafter and because the continuation of increased blood glucose variations for a long period is rare since interventions are often implemented. To our knowledge, there has been no report on the day-to-day GV.

In recent years, there has been an increasing number of reports on long-term GV [17, 18, 39, 42, 53-56], and a sub-analysis of the ADVANCE trial [52] reported that outpatient blood glucose variations and HbA1c variations are involved in diabetic complications and mortality rates. Summary of the possible explanations of the factors affecting the glycemic variability is illustrated in Figure 1. However, a method to measure long-term GV has not been established, and measurement frequencies vary from once to 12 times per year. Although many studies conducted those measurements once every 3 months, additional studies would be required to assess whether accurate fluctuations are observed because of seasonal fluctuations in HbA1c. In addition, that there are various factors involved in the GV is problematic, such as drug changes during the observation period, whose effects cannot be excluded in practice, making interpretation of the results difficult. Moreover, due to lack of a clear definition of long-term GV, the observation period in these studies on long-term GV varied considerably, ranging from 1 to 10 years, and most of the studies were from 2 to 3 years. Furthermore, when evaluating long-term GV, a longer observation period may not always be better for evaluation because the possibility of deterioration of the patient's condition due to the disease progression and hospitalization may increase. In addition, differences in the contribution to the prognosis between long-term GV and the mean HbA1c value are still unknown, which also needs to be investigated.

## Conclusions

Types of GV in terms of time frame vary from short-term to long-term. Several studies reported that long-term GV was related to micro- and macro-angiopathies in patients with type 2 diabetes mellitus (T2DM). However, there are still unknown aspects regarding the relationships of various durations of GV with prognosis. Further clinical trials are required that focus on the mechanism of GV and that evaluate whether GV can be a valuable therapeutic target for patients with T2DM.

## Conflict of Interest

The authors of this manuscript have the following competing interests: M.S. has participated in speaker's bureaus/advisory panels for Sanofi, Daiichi-Sankyo, Astellas, and Tanabe-Mitsubishi.

## Abbreviations

GV: glycemic variability; CGM: continuous glucose monitoring; MAGE: mean amplitude of glycemic excursions; MODD: mean of daily difference; OGTT: oral glucose tolerance test; BRS: baroreflex sensitivity; T2DM: type 2 diabetes mellitus

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