DIABETES & METABOLISM JOURNAL

How Can We Easily Measure Glycemic Variability in Diabetes Mellitus?

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Glycemic monitoring is essential for the management of diabetes mellitus. Today, glycosylated hemoglobin (HbA1c) is the most widely used parameter for glycemic monitoring and reflects average glucose levels over 2 to 3 months. However, HbA1c is limited in its ability to reflect short-term glycemic changes. Also, it cannot separately reflect postprandial hyperglycemia (PPH) and fasting hyperglycemia. In addition, HbA1c is a not a good predictor of hypoglycemic episodes as it only accounts for 8% of the probability of severe hypoglycemia [1,2].

A growing body of evidence suggests that PPH and glycemic variability (GV) may be independent risk factors for macrovascular complications in patients with diabetes [3]. The relationship between PPH and cardiovascular disease (CVD) has been consistently reported even in the context of HbA1c levels in the nondiabetic range [4].

Many experimental animal studies indicate that GV, compared with chronic hyperglycemia, promotes excess oxidative stress and worsens cellular and vascular damage [3]. Although the effect of GV on oxidative stress in clinical settings remains controversial, several studies have also confirmed these findings in human studies. Few studies have demonstrated the effect of daily GV on CVD outcomes, although visit-to-visit GV, a longer term index, may predict worse CVD outcome in patients with diabetes.

Although GV usually refers to overall glycemic variation including hyper and hypoglycemia, GV is often also used to refer to postprandial glycemic excursion. Complete differentiation between GV and PPH may be impossible because they are correlated with each other, but GV is thought to be important as it is associated with hypoglycemia, especially severe hypoglycemia [5,6]. Severe hypoglycemia can not only directly cause death, but also predict higher risk of mortality, CVD or severe arrhythmia [3].

Especially, patients with type 1 diabetes mellitus (T1DM) are frequently exposed to both excessive hyperglycemia and prolonged, dangerous hypoglycemia even with the availability of insulin pumps and short and long-acting insulin analogs [7]. Thus, clinically, monitoring and minimizing GV is important for preventing hypoglycemia and CVD, in management of diabetes mellitus.

There are many measures of GV, extensively reviewed by Rodbard [8]. The most simply used method to assess variability is standard deviation (SD) which is a measure of dispersion of glucose, but its meaning is insufficient in "not" normally distributed data. Mean amplitude of glycemic excursions (MAGE) by Service and colleagues [9], mean of daily differences, and several other measures are commonly used to evaluate GV. However, measurement of GV is challenging because it is still relatively new and most of these measures for GV are calculated from continuous glucose monitoring system (CGMS) [10]. In fact, CGMS is the most reliable and precise method for evaluating GV and PPH. However, it is inconvenient and not easily accessible in general practice.

Recently, easily measurable glycemic biomarkers, such as 1,5-anhydroglucitol (1,5-AG), glycated albumin (GA) and fructosamine (FA) have been reported to reflect GV and PPH in T1DM and type 2 diabetes mellitus (T2DM) with various glycemic control status [11-13].

In this issue of Diabetes & Metabolism Journal, Seok et al. [14] reported that 1,5-AG may be a useful marker for assessment of short-term change of glycemic excursion in patients with T1DM. This study showed that the changes of 1,5-AG levels for the period of 2 weeks is negatively correlated with the changes of various CGMS parameter for GV and PPH. Nonetheless, these results are significant only in moderately controlled T1DM with baseline mean CGMS glucose <180 mg/dL and not in poorly con-

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trolled T1DM. Authors suggest that 1,5 AG may have clinical implication for the management of glycemic excursion in T1DM.

1,5-Anhydroglucitol is a good marker of PPH but had a limitation as a marker of GV until now. Dungan et al. [11] performed a study on 40 patients with T1DM and T2DM which revealed a significant negative correlation between 1,5-AG and PPH in patients with moderate glycemic control. It was reported that 1,5-AG was significantly correlated with GV under various study conditions, including well controlled diabetes [15,16]. In contrast, Kim et al. [12] suggested that 1,5-AG did not correlate with GV and oxidative stress (8-iso PGF2α) but only correlates with mean glucose and PPH in patients with moderately controlled diabetes (HbA1c <8%). Chon et al. [13] also reported that 1,5-AG may have limited value for assessing GV in patients with well-controlled T2DM and reflects PPH more robustly than FA or HbA1c. Therefore, the importance of 1,5-AG, which responds most sensitively to PPH or postprandial variability, can be further emphasized. In consistent with these results, Seok et al. [14] reported that changes of 1,5-AG are significantly correlated with the changes of all PPH indexes such as mean post-meal maximum glucose, AUC-180 and mean glucose in moderately controlled T1DM. However the correlation with GV indexes, MAGE and lability index, showed a borderline significance.

FA primarily represents GA, as it is the most abundant protein present. FA and GA levels were reported to be strongly correlated with each other [17]. Recent studies reported that GA reflect not only the average glucose level, but also glucose fluctuations and postprandial glucose excursions [18]. FA rather than 1,5-AG which is correlated with MAGE in well controlled T2DM [13]. Because GA levels increase as blood glucose levels rise and the rate of GA level increase is 10 times faster than that of hemoglobin, serum GA levels may also be affected by temporary blood glucose spikes [13]. However, the exact reasons why FA and GA are related to daily glycemic excursions remain unclear.

Until now, there has been no conclusive evidence which is the best biomarker for assessing GV in diabetes in various glycemic control status. In addition, clinical evidence is limited on the association between the changes of these biomarkers and those of GV and PPH indexes during treatment. Mean levels of glucose, HbA1c, and GA may all reflect the fasting state, postprandial state, and variability in patients with moderate or poor diabetes control. 1,5-AG may be useful for monitoring PPH, but when marked hyperglycemia persists (HbA1c >8%) 1,5-AG level becomes too low to be used as a marker of glycemic excursion. Considering recent studies, 1,5-AG can reflect GV in T1DM and T2DM, but it has limited ability in well or moderately controlled patients with glycemic excursions with narrow ranges. More study is needed to find a valid biomarker for assessing GV and application to diabetes treatment in clinical practice.

CONFLICTS OF INTEREST

ACKNOWLEDGMENTS

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