COMMENTARY

Assessment of Interday Glucose Variability in Type 2 Diabetes

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Introduction

IN HEALTHY PEOPLE, fasting plasma glucose is maintained in a tight normal range and postprandial glucose also varies within a tight range despite varying composition and amount of meals and extent and timing of physical activity.^{1–3} Glycemic control is abnormal in diabetes mellitus (DM) with untreated DM characterized by persistent hyperglycemia. Since type 1 diabetes (T1D) is characterized by little or no endogenous insulin secretion, hyperglycemia may be rapidly fatal in the absence of insulin therapy.

Insulin therapy without simultaneous use of continuous glucose monitoring (CGM) in T1D results in unacceptable daily glucose variability (GV) with considerable percentage of time spent daily in hypo- and hyperglycemic range (<70 and >180 mg/dL, respectively). Therefore, for the past 70 years, many mathematical measures have been proposed to measure GV, many in the pre-CGM availability era.^{1,4,5} These GV measures have been described for intraday GV or less commonly for interday variability.² A measure of GV for interday variability was first proposed about 45 years ago but has been reported to a limited extent in clinical studies.

To our knowledge, the only measure of interday variations in glycemic control is based on the mean of daily difference (MODD). MODD is the average of difference between glucose concentrations at the same time points during 2 or more successive days. Higher MODD values indicate more GV between days. GV is higher in T1D than in type 2 diabetes (T2D) and has mostly been studied in T1D.⁵ T2D is much more prevalent than T1D and glucose control in T2D continues to be suboptimal worldwide. Therefore, with maturation of CGM technology facilitating GV assessment, GV is being reported as a post hoc end point in T2D studies recently.

In this issue of the journal, Iuchi et al. report the results of a randomized, open label crossover study of Lantus and Glargine U300 on MODD in 22 subjects with T2D.⁶ Subjects were randomized either to glargine U100 or U300 for 4 weeks with changes to insulin dosing made initially and after 2 weeks. iPro2 CGM device (Medtronic, Northridge, CA)

was used for 72 h at the end of each 4-week period to assess GV. They describe GV with multiple intraday (coefficient of variation [CV], mean amplitude of glucose excursion [MAGE], and net glycemic action at 2-h time intervals [CONGA-2]) measures and MODD. The reasons why these measures of intraday GV are chosen for reporting are not mentioned in the article. Many more measures of intraday GV have been described, and summarized recently.^{1,5} Despite HbA1c being similar at the end of the two study periods, MODD showed significant decrease with U300 glargine treatment. There may be multiple reasons for improvement in MODD on U300 glargine. The most important reason could well be the longer duration of action of U300.

Confounding factors include adherence to insulin therapy. Confirmation of insulin administration at the prescribed time based on patient self-reported diary or use of an insulin pen with memory function would have provided a hierarchy of reasons for improvement in MODD in this clinical trial. Important information about the CGM signal such as extent of missing data and mean absolute difference is also not provided.

The findings reported by Iuchi et al.⁶ contribute to the current debate about which measures to use to assess intraday and interday GV in the context of management of T2D but also in the wider context of DM. Other studies have reported MODD based on CGM data in T2D patients (Table 1). MODD was observed to be high in newly diagnosed subjects with T2D than controls as shown by Zhou et al.⁷ Similarly, T2D patients with diabetic neuropathy showed higher MODD than patients with no neuropathy despite similar HbA1c values in the two cohorts.⁸ More recently, Ohara et al. showed that high MODD values were associated with oxidative stress in patients with T2D.⁹ Possible explanations for high MODD in T2D include variability in interday life style factors such as macronutrient intake and physical activity/exercise on the one hand and adherence to antihyperglycemic medications on the other. The former could be captured with online food diary apps and physical activity capture devices (accelerometers) and the latter with insulin pens including memory function and medication containers with sensors

TABLE 1. MEAN OF DAILY DIFFERENCE REPORTING IN CLINICAL STUDIES

Study	Duration of study (days)	Study design and intervention	Type of CGM use	Outcome	Duration for which MODD analyzed (days)	Comments
Molnar et al. ²	2	Continuous blood glucose analysis in stable, unstable diabetics, and normal controls.	Continuous blood glucose analyses.	Higher MODD values with unstable diabetes.	2	MODD was proposed as a measure. Drawback: no CGM used.
Zhou et al. ⁷	30	3 days of CGM use in newly diagnosed T2D and healthy subjects In subcohort with HbA1c >8.5% MDI use for 2–3 weeks Again CGM use for 3 day.	Medtronic MiniMed iPro	MODD was high in newly diagnosed T2D than in controls.	3	Day-to-day GV was high in newly diagnosed T2D than in normal controls.
Xu et al. ⁸	3	Group 1: T2D with DPN (HbA1c <7.0%) Group 2: T2D without DPN (HbA1c <7.0%)	Medtronic MiniMed (system not specified).	T2D subjects with DPN had higher MODD values.	3	Important association of day-to-day GV measured with MODD to DPN.
Ohara et al. ⁹	3	T2D subjects wore CGM for 72 h.	Medtronic MiniMed iPro2®	Oxidative stress associated with MODD.	3	Oxidative stress was measured using a d-ROMs test.
Mori et al. ¹¹	7	Subjects with T1D and T2D wore CGM for 7 days.	Medtronic iPro2	MODD was significantly higher in subjects with higher variability in lifestyle.	7	Patient's characteristics, GV, and lifestyle variability are important factors to consider.

CGM, continuous glucose monitoring; DPN, diabetic peripheral neuropathy; d-ROMs, diacron-reactive oxygen metabolites; GV, glucose variability; MDI, multiple daily injections; MODD, mean of daily difference; T1D, type 1 diabetes; T2D, type 2 diabetes.

confirming medication bottle opening and more sophisticated systems such as insulin pumps.

An additional factor such as the presence of insulin secretory reserve could also influence MODD.¹⁰ Recently Mori et al. reported that MODD values were associated with variability in interday life style in people with T2D (Table 1). MODD was higher in people with higher interday variability in life style than in those with limited variability in lifestyle.¹¹ It is also important to consider factors related to the CGM signal itself such as duration of CGM use being analyzed for reporting, reliability of the signal during the same period, and use of medications affecting the CGM signal itself such as acetaminophen.^{12,13} A recently published article suggests that at least 2 weeks of CGM data are needed to observe the impact of any intervention on GV.¹⁴

It is important to note that when proposed originally, MODD involved measurement of glucose values for 2 consecutive days. However, with introduction of CGM and improvements in computing capabilities, several days of data

can be used to calculate MODD. In 2009, Rodbard utilized several days of glucose data to compute MODD_d, a modified measure to describe interday GV using CGM data for many days.¹⁵ Going forward, studies addressing all of the factors already discussed would take us into more rigorous analyses of GV and development and testing of interventions to improve GV. We searched www.clinicaltrials.gov for current studies evaluating GV as an end point of interest, but use of MODD as an a priori listed end point seems to be limited.

In conclusion, the description of MODD in the context of a clinical trial of intervention in T2D is an important report further opening up the field of studying and improving CGM-based intra- and interday GV. Such studies would potentially improve safe and effective use of anti-hyperglycemic therapies.

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Author Disclosure Statement

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