COMMENT ON LACHIN ET AL.

Association of Glycemic Variability in Type 1 Diabetes With Progression of Microvascular Outcomes in the Diabetes Control and Complications Trial. Diabetes Care 2017;40:777–783

Jesper Fleischer,[1]
Simon Lebech Cichosz,[2]
and Troels Krarup Hansen[1]

Diabetes Care 2017;40:e164 | https://doi.org/10.2337/dc17-1339

Inspired by the interesting study from Lachin et al. (1), we performed post hoc analyses of existing data from two of our recent clinical studies (2,3) to investigate the possible association between the glycemic variability parameter mean amplitude of glycemic excursions (MAGE) calculated from either self-monitoring of blood glucose (SMBG) or continuous glucose monitoring (CGM) devices. In both studies, all patients were equipped with a CGM device and instructed to perform SMBG measurements for 3 days in a row. In the first study (2), 21 patients with type 1 diabetes performed seven blood glucose measurements each day. Our post hoc analysis showed no correlation between $MAGE_{SMBG}$ and $MAGE_{CGM}$, $R^2 = 0.15$ ($P = 0.67$). In the second study (3), 87 patients with type 2 diabetes performed four blood glucose measurements each day. The post hoc analysis of this study showed a weak correlation between $MAGE_{SMBG}$ and $MAGE_{CGM}$, $R^2 = 0.26$ ($P < 0.05$).

The study by Lachin et al. (1) adds to the important discussion of whether it is possible to use spot glucose measurements to estimate variability in a time series. The main problem with spot measurements is the limited number of values, and even if as many as seven SMBG measurements are performed every day, there will always be significant blind areas in between measurements. Continuous data recording with measurements every 1–5 min eliminates this problem and is therefore an important improvement in measurements of the glycemic profile (4). It is also well known that there are significant interindividual and intraindividual variations in 24-h glucose profiles, especially during the postprandial glycemic peak time. In line with this, we have just shown that it is only possible to find the real postprandial glycemic peak by using data from CGM devices (4).

Furthermore, it is important to be cautious when using statistical algorithms like multiple imputation to estimate missing data points from a time series (5). Traditional multiple imputation algorithms fail to take information from just before and just after the missing data point into consideration. The lack of information close in time to the missing spot glucose measurement makes the statistical multiple imputation algorithm very difficult to construct. Lachin et al. (1) used indirect variables like quarterly HbA_{1c} and BMI and the annual total insulin dose as input to the imputation algorithm for imputing missing data in the time series of glucose measurements. Adding these variables may greatly increase the statistical model validity but may also reduce the variability of the time series data. It would have been interesting to know whether HbA_{1c}, which is part of the input to the Lachin et al. (1) statistical model, is associated with $MAGE_{SMBG}$.

In conclusion, we found no association between MAGE calculated from SMBG and MAGE calculated from CGM devices in type 1 diabetes. Considering this, as well as the inherent weakness of the multiple imputation algorithm to estimate missing data points in a time series, we believe one should be cautious in ruling out a role of within-day glycemic variability in the development of microvascular complications based on studies with only SMBG data available.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

References

1. Lachin JM, Bebu I, Bergenstal RM, et al.; DCCT/EDIC Research Group. Association of glycemic variability in type 1 diabetes with progression of microvascular outcomes in the Diabetes Control and Complications Trial. Diabetes Care 2017;40:777–783
2. Cichosz SL, Frystyk J, Tarnow L, Fleischer J. Combining information of autonomic modulation and CGM measurements enables prediction and improves detection of spontaneous hypoglycemic events. J Diabetes Sci Technol 2015;9:132–137
3. Fleischer J, Cichosz SL, Hoeyem P, et al. Glycemic variability is associated with reduced cardiac autonomic modulation in women with type 2 diabetes [published correction appears in Diabetes Care 2015;38:2188]. Diabetes Care 2015;38:682–688
4. Fleischer J, Laugesen E, Cichosz SL, et al. Continuous glucose monitoring adds information beyond HbA1c in well-controlled diabetes patients with early cardiovascular autonomic neuropathy. J Diabetes Complications 2017;31:1389–1393
5. Zhang Z. Multiple imputation for time series data with Amelia package. Ann Transl Med 2016;4:56

[1]*Department of Endocrinology and Internal Medicine and Medical Research Laboratories, Aarhus University Hospital, Aarhus, Denmark*
[2]*Department of Health Science and Technology, Aalborg University, Aalborg, Denmark*

Corresponding author: Jesper Fleischer, jesper.fleischer@clin.au.dk.