



RESPONSE TO 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.

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Fleischer et al. (1) contend that discrete blood glucose measurements such as those in the 7-point profile in the Diabetes Control and Complications Trial (DCCT) fail to provide an accurate measure of mean amplitude of glycemic excursions (MAGE). However, this is not borne out by their post hoc analysis of the two studies cited (their refs. 2 and 3) related to autonomic modulation. It is unclear which of the many SMBG measurements performed each day (ref. 2) were selected as the seven values used to calculate MAGE. The design of the study made it unlikely that they were carefully timed premeal and 90 min post-meal. The use of three (premeal) and bedtime SMBG results in ref. 3 precludes a reliable calculation of MAGE.

The broader issue of whether discrete blood glucose values can provide as reliable a measurement of MAGE as continuous glucose monitoring (CGM) was addressed in our article (2). What is overlooked in this controversy is that the DCCT did not rely on SMBG but on central laboratory-measured blood glucose from timed capillary collections. CGM differs not only in frequency but in the site of sampling. Moreover, for a

three meal per day routine, only six blood glucose values usually enter into the calculation of MAGE. When 7 vs. 22 blood glucose values were compared in the calculation of MAGE, there was a significant correlation (3) supporting the 7-point profile.

Also, it is statistically inaccurate to refer to the DCCT quarterly 7-point glucose profile data as a time series. Rather, we have a vector of up to seven observed values from each quarterly profile that are assumed to be multivariate normal. It is then straightforward to compute the multiple imputations as explicitly described in the Supplementary Data. The imputation method used information collected at each quarterly visit as well as that from all other quarterly visits.

There is no question that CGM provides more accurate estimates of the degree of diurnal variation than a 7-point glucose profile, as stated in the discussion of our article. On the other hand, there is no other data set that provides the repeated measures of daily glycemia and long-term outcomes. We agree that our data do not definitively rule out a role of within-day glycemic variability, largely owing to the reliance on blood glucose

profile data. However, as stated in our article, our results, based on extensive data carefully collected over time, fail to provide support to the hypothesis that within-day variability plays an apparent role in the development of microvascular complications.

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