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The Effect of Glucose Variability on the Risk of Microvascular Complications in Type 1 Diabetes

Response to Kilpatrick et al. and Bolli

The article by Kilpatrick et al. (1) used data from the Diabetes Control and Complication Trial to investigate the relationship between glycemic variability and the subsequent development of diabetes complications. They report that glucose variability, as measured by a quarterly eight-point glucose profile (excluding the 3 A.M. value because of limited data), was not associated with development or progression of retinopathy or nephropathy. An accompanying editorial by Bolli (2) highlights the potential clinical impact of this finding, stating that "the instant blood glucose at a given time of day is not important, and it does not matter if it is high or low either before or after meals (or vice versa) as long as A1C is at the target value <7.0%."

We believe that these results, and the clinical recommendations that have sprung from them, should be interpreted with caution. While the Diabetes Control and Complication Trial database is large and its data regarding complications extraordinary, quarterly seven-point glucose profiles are unlikely to fully reflect true glycemic variation in these subjects with type 1 diabetes.

Continuous glucose monitors provide the opportunity to capture the magnitude of glycemic variation far better than seven-point glucose profiles. The Diabetes Research in Children Network (DirecNet) Study Group (3) compared simultaneous eight-point glucose profiles over three days with near continuous glucose profiles (values every 5 min) using Medtronic-Minimed CGMS in 161 children and adolescents with type 1 diabetes. The eight-point glucose profiles were measured using One Touch UltraSmart (LifeScan) meter, a device shown to be quite accurate (4). The meal-related glucose excursion measured using eight-point testing was calculated by subtracting premeal from postmeal glucose. The analogous glucose excursion measured with continuous glucose self-monitoring (CGMS) was calculated as the difference between the premeal CGMS value (corresponding to the time of the eight-point test) and the peak value (within 3 h of the premeal eight-point test). Postprandial excursions were two to three times larger when measured by the CGMS than by eight-point testing. These findings are not surprising as it is unlikely a single glucose measurement would coincide with the postmeal peak. Moreover, a single measurement cannot measure the duration of the postmeal glucose rise.

Given that glucose profiles based on single point-in-time postprandial measurements are a suboptimal measure of glycemic variability, we believe it is premature to discount the potential clinical importance of reducing glycemic variability. Further studies using continuous glucose data will be needed to finally answer this important question.

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The Effect of Glucose Variability on the Risk of Microvascular Complications in Type 1 Diabetes

Response to Kilpatrick et al.

In an analysis of the datasets collected in the Diabetes Control and Complications Trial, Kilpatrick et al. (1) reported that mean blood glucose was predictive of microvascular complications in patients with type 1 diabetes, while glucose variability did not appear to be a factor in their development. We question their methodology and thereby also the conclusions. They calculated the variability of within-day blood glucose as the SD around the mean of a seven-point glycemic profile measured at each patient's quarterly visit. With such a methodology, they have probably not selected major glucose fluctuations, but rather a composite of both major and minor fluctuations, and most of them were likely to be minor. Furthermore, they have probably blunted the contribution of major glucose fluctuations, as it is not likely that the four pre- and interprandial and three postprandial glucose values included in the seven-point profile were in perfect coincidence with the nadirs and peaks of glucose, respectively. In contrast, the mean amplitude of glycemic excursions (MAGE) described by Service et al. (2) are designed to quantify major swings of glycemia and to exclude minor ones, since its measurement is obtained by calculating the differences between consecutive peaks or nadirs and includes only those greater than the SD of mean glycemic values. Indirect evidence for this is given by observations from the study of Monnier et al. (3). By further analyzing their data, they first found that the MAGE value in 21 patients with type 2 diabetes was much greater (75 mg/dl) than the SDs of within-day blood glucose calculated from seven-point glycemic profiles (37 mg/dl). Second, the activation of oxidative stress, as estimated from urinary excretion rates of isoprostanes, was highly correlated with MAGE calculated from continuous monitoring of glucose in the interstitial fluid ($r = 0.85$; $P < 0.0001$) (3). A deterioration of this relationship ($r = 0.43$;

$P = 0.05$) was observed when SDs of seven-point glycemic profiles were substituted for MAGE values.

Even though the MAGE determination requires continuous glucose monitoring, we believe that this parameter should be the "gold standard" for assessing glucose fluctuations in all prospective interventional studies designed to estimate glucose variability. We therefore believe that additional studies are required to definitively determine the role of glycemic variability in the pathogenesis of the micro- and macrovascular complications of diabetes. Even though the technology of continuous measurements of glucose in interstitial fluid remains a subject of debate, the use of continuous glucose sensors might be useful for conducting such trials.

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The Effect of Glucose Variability on the Risk of Microvascular Complications in Type 1 Diabetes

Response to Kilpatrick et al.

We have read with interest the article by Kilpatrick et al. (1), which reports the lack of effect of glucose variability on the risk for microvascular complications in type 1 diabetes using the Diabetes Control and Complications Trial database. We are pleased that the authors came to the same conclusions as we did in our examination (2) of this question using the same database. Since Diabetes Control and Complications Trial subjects were studied for differing durations and not all subjects provided complete seven-point glucose samples, how were these factors dealt with in the analysis? Furthermore, what were the reasons to limit the assessment of glucose variability to SD and omit measurements of M value and mean amplitude of glycemic excursion, two established indexes of glucose variability? The authors may wish to reexamine their literature research technique; it appears to be less than rigorous.

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The Effect of Glucose Variability on the Risk of Microvascular Complications in Type 1 Diabetes

Response to Kilpatrick et al. and Bolli

We read with interest the article by Kilpatrick et al. (1) and the accompanying editorial by Bolli (2). While the analysis of seven-point glucose profiles reported in this study (1) suggested that glucose variability is not an independent risk factor for microvascular complications, the seven-point profile may not be an accurate representation of true glycemic variability as measured by continuous blood glucose monitoring (3). Although there are not enough data at present to justify new treatment guidelines based on glycemic variability, there certainly are important published data (3) showing that glycemic variability leads to greater oxidative stress. Since increased intracellular superoxide production has been shown to initiate a large number of hyperglycemia-induced mechanisms related to the pathogenesis of diabetic complications (4), we believe that further investigation of the hypothesis that increased glycemic variability is a risk factor for diabetic complications is warranted.

Indeed, it was not that long ago that there was widespread doubt in the medical community that increased levels of hyperglycemia were a risk factor for diabetic complications (5). However, this doubt was addressed by further clinical research (6).

A little-noticed but very important observation published (6) by the Diabetes Control and Complications Trial Research Group >10 years ago was that sub-