later years, the initial large difference almost disappeared; i.e., metabolic control improved significantly more in patients using SMBG than in nonusers (4). Similarly, in the Kaiser Permanente cohort, there was an improvement of A1C by ~0.6% after initiation of SMBG, whereas A1C deteriorated by 0.2% in nonusers. These opposing changes were also observed after adjustments for change of type of antidiabetic medication or other potential confounders (3).

This concordance of observational studies on three different continents is remarkable. In the real world, SMBG appears to be preferentially used by younger patients who exhibit worse than average metabolic control, and the initiation of SMBG is followed by improved metabolic control.

Hubert Kolb, phd[1]
Berthold Schneider, phd[2]
Lutz Heinemann, phd[3]
Volker Lodwig[4]
Stephan Martin, md[1]

From the [1]German Diabetes Center at the Heinrich-Heine University, Düsseldorf, Germany; the [2]Institute of Biometry, Medical University of Hannover, Hannover, Germany; the [3]Profil Institute for Metabolic Research, Neuss, Germany; and the [4]Institute for Medical Informatics and Biostatistics, Basel, Switzerland.

Address correspondence to Hubert Kolb, German Diabetes Center, Auf'm Hennekamp 65, D-40225 Düsseldorf, Germany. E-mail: hubert.kolb@uni-duesseldorf.de.

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Is Self-Monitoring of Blood Glucose Appropriate for All Type 2 Diabetic Patients? The Fremantle Diabetes Study

Response to Kolb et al.

Despite the negative results of our community-based study of the link between self-monitoring of blood glucose (SMBG) and glycemia (1), Kolb et al. (2) commented on the overall concordance of our study and several other observational studies. They also suggest that we might have missed a positive impact of SMBG since new users in our cohort were not differentiated from either prevalent users or never users.

In our prospectively followed 531 type 2 diabetic patients (1), 92 who self-monitored at study entry stopped without subsequent detriment to their A1C (median [interquartile range] 7.0% [6.3–8.0] vs. 7.3% [6.4–8.4] at annual visits before and after stopping, respectively; mean change +0.1%; $P = 0.47$). By contrast, 103 patients who started SMBG during follow-up improved their A1C (7.5% [6.3–9.1] vs. 7.2% [6.2–8.4] before and after, respectively; $P = 0.032$). The mean change (−0.3%) is similar to that in both the new-user cohort of Karter et al. (3) and the meta-analysis of the few randomized controlled trials of SMBG (4).

The remaining 336 patients either performed SMBG throughout follow-up (SMBG+; $n = 306$) or did not (SMBG−; $n = 30$). We calculated updated mean A1Cs over 5 years for patients in these two groups by baseline diabetes treatment. For diet-treated subjects, the medians were 6.6% (interquartile range 5.9–7.1) for SMBG+ ($n = 92$) and 6.6% (5.9–7.0) for SMBG− ($n = 17$). For those taking oral hypoglycemic agents (OHAs), the medians were 7.4% (6.8–8.2) ($n = 181$) and 7.0% (6.5–7.5) ($n = 13$), respectively ($P = 0.24$). All 33 insulin-treated patients who were not performing SMBG at baseline monitored at some time during follow-up.

Previously, we have shown in the same longitudinal cohort of 531 patients (5) that the median A1C was reduced by 0.3% when diet-treated patients started OHA and by 1.5% when OHA-treated patients started insulin. The apparent benefit of initiating SMBG might, therefore, reflect intensification of treatment. However, when our patients started SMBG, 85% continued with the same treatment, 12% reduced treatment, and 3% intensified treatment.

The largest randomized controlled trial (6) has found that the glycemic improvement observed in non–insulin-treated patients allocated to SMBG occurred in the first 3 months, with a steady state thereafter. These and our longer-term data suggest that SMBG may have only a relatively transient beneficial effect on glycemia. There is a need for strategies that ensure its sustainability.

Wendy A. Davis, phd
David G. Bruce, md
Timothy M.E. Davis, d phil

From the School of Medicine and Pharmacology, Fremantle Hospital, University of Western Australia, Fremantle, Australia.

Address correspondence to Dr. W.A. Davis, School of Medicine and Pharmacology, Fremantle Hospital, P.O. Box 480, Fremantle, Western Australia 6959. E-mail: wdavis@cyllene.uwa.edu.au.

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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.

THE DIABETES RESEARCH IN CHILDREN NETWORK (DIRECNET) STUDY GROUP

Address correspondence to Darrell Wilson, MD, c/o DirecNet Coordinating Center, Jaeb Center for Health Research, 15310 Amberly Dr., Suite 350, Tampa, FL 33647. E-mail: direcnet@jaeb.org.

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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 ($r = 0.43$;