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

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OBJECTIVE — It is not known whether glycemic instability may confer a risk of microvascular complications that is in addition to that predicted by the mean blood glucose (MBG) value alone. This study has analyzed data from the Diabetes Control and Complications Trial (DCCT) to assess the effect of glucose variability on the risk of retinopathy and nephropathy in patients with type 1 diabetes.

RESEARCH DESIGN AND METHODS — Pre- and postprandial seven-point glucose profiles were collected quarterly during the DCCT in 1,441 individuals. The mean area under the curve glucose and the SD of glucose variability within 24 h and between visits were compared with the risk of retinopathy and nephropathy, having adjusted for age, sex, disease duration, treatment group, prevention cohort, and phase of treatment.

RESULTS — Multivariate Cox regression showed that within-day and between-day variability in blood glucose around a patient's mean value has no influence on the development or progression of either retinopathy ($P = 0.18$ and $P = 0.72$, respectively) or nephropathy ($P = 0.32$ and $P = 0.57$). Neither preprandial ($P = 0.18$) nor postprandial ($P = 0.31$) glucose concentrations preferentially contribute to the probability of retinopathy.

CONCLUSIONS — This study has shown that blood glucose variability does not appear to be an additional factor in the development of microvascular complications. Also, pre- and postprandial glucose values are equally predictive of the small-vessel complications of type 1 diabetes.

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It is well established that the risk of developing the microvascular complications of diabetes is intimately related to the glycemic control of an individual. Having determined that HbA_{1c} (A1C) could be used as a surrogate marker for glycemia (1), both the Diabetes Control and Complications Trial (DCCT) in type 1 diabetes and the U.K. Prospective Diabetes Study in type 2 diabetes confirmed an exponential relationship between rising blood glucose and the risk of either developing or worsening retinopathy, nephropathy, and neuropathy (2–5). What is less clear is whether glycemic instability may confer a risk to complications that is in addition to that predicted by the mean glucose value alone. It is therefore unknown if two individuals with the same mean blood glucose (MBG), but extremes of glucose variability, might be expected to have the same or different complication risks.

Circumstantial evidence from different studies gives conflicting conclusions as to whether variability in glucose values adds to the likelihood of complications. In favor of this association is the fact that in the DCCT, the rate of complications at a given value of A1C was higher in the conventionally treated patients than in those intensively treated (3). It was suggested that this may be a consequence of larger glycemic excursions in the former group of patients since they were on fewer injections of insulin per day. Also in support is another study where the incidence of retinopathy in a group of adolescents with type 1 diabetes appeared to fall substantially between 1990 and 2002, despite A1C levels changing little throughout the study period (6). It was again felt that the move to multiple injection regimes over the time period may have contributed to this improvement by reducing glycemic fluctuations rather than the mean glucose concentration. It has therefore been proposed that beyond simply avoiding short-term complications such as hypoglycemia and diabetic ketoacidosis, minimizing variability in blood glucose control should be a therapeutic goal for patients to help avoid any excess risk of long-term complications as well (7). More recently, however, it has been shown that the variability of blood glucose seems to have little influence on the A1C of a patient over the mean glucose value, but it is not known if this translates to a similar risk of complications (8).

In a related issue, there is firm evidence that postprandial glycemia is a stronger risk marker for the large-vessel (macrovascular) complications of diabetes than fasting or preprandial concentrations (9,10). Indeed, many treatments for diabetes now focus on reducing glycemic excursions following meals in the belief that they may preferentially help reduce the incidence of cardiovascular disease in this high-risk group of patients (11). However, little is known about the relative contribution of pre- and postprandial glycemia to the likelihood of developing microvascular complications. As a consequence, this gap in knowledge has been seen as a priority for further research (12).

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Abbreviations: AER, albumin excretion rate; AUC, area under the curve; DCCT, Diabetes Control and Complications Trial; MBG, mean blood glucose.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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See accompanying editorial, p. 1707.

Table 1—*Univariate Cox regression models relating glycemia to microvascular complications*

Variable	Nephropathy	*P* value	Retinopathy	*P* value
MBG (AUC)	1.04 (0.97–1.11)	0.26	1.16 (1.08–1.25)	<0.0001
SD MBG (AUC)	0.97 (0.83–1.13)	0.70	0.99 (0.83–1.18)	0.92
SD (within day)	1.01 (0.99–1.03)	0.20	1.03 (1.01–1.05)	0.02
Preprandial mean	1.07 (0.99–1.45)	0.09	1.19 (1.10–1.29)	<0.0001
Postprandial mean	1.05 (0.98–1.12)	0.19	1.17 (1.09–1.26)	<0.0001

Data are HR (95% CI). MBG (AUC), AUC of seven-point blood glucose profile (mmol/l); SD MBG (AUC), SD of between-visit AUC; SD (within-day), SD of glucose profile.

The publicly available DCCT database has provided a means for investigating these questions more closely, since the 1,441 participants with type 1 diabetes had 1-day glucose profiles (including pre- and postprandial measurements) performed quarterly by a laboratory and had assessments closely detailing any development or progression of small-vessel complications. This current study has therefore analyzed the DCCT data to determine the relative contribution of pre- and postprandial glycemia to the development of microvascular complications and also to establish whether the degree of instability of glucose control has any additional influence on this risk.

RESEARCH DESIGN AND METHODS

The datasets

We used the publicly accessible datasets collected by the DCCT, which were stored in SAS format (available at www.gcrc.umn.edu). The DCCT was a 9-year follow-up study of 1,441 participants with type 1 diabetes comparing the effect of intensive versus conventional blood glucose management on the development of microvascular complications of diabetes. At randomization, patients were stratified into one of two cohorts. The primary prevention cohort ($n = 726$) had no evidence of retinopathy by fundus photography and a urinary albumin excretion rate (AER) <40 mg/24 h (28 μg/min). The secondary prevention cohort ($n = 715$) had only minimal retinopathy and a AER <200 mg/24 h (140 μg/min). The study participants were randomized into intensive ($n = 711$) and conventional ($n = 730$) treatment groups.

Definition of events

Severity of retinopathy was determined by the 25-point Early Diabetic Retinopathy Treatment Study interim score (2). The development and progression of sustained retinopathy was defined as a change from baseline of three or more units on the Early Diabetic Retinopathy Treatment Study score on any two successive annual evaluations. During the 9 years of follow-up, 242 people developed sustained retinopathy, 67 of whom were in the intensive treatment group. Nephropathy was defined as an increase in AER ≥40 mg/24 h (28 μg/min) on any annual evaluation providing that the baseline AER was <40 mg/dl (28 μg/min) (13). The mean age was 27 years (range 13–39). Just over half ($n = 761$, 52.8%) were men. Average BMI was 23.4 kg/m^2; <2% had a BMI >30 kg/m^2. Nearly all participants were Caucasian. The median disease duration was 4 years. Approximately one-fifth declared themselves as current smokers.

To have as complete a dataset on each patient as possible, we based our analyses on the data up to 5 years since the majority of those lost to follow-up defaulted after this time. At 5 years, 94 participants had retinopathy, 126 had nephropathy, and 189 had either retinopathy or nephropathy.

Glycemic variables and statistical methods

A blood glucose profile was taken at 3-monthly intervals. Blood glucose was assessed at seven points throughout the day, namely, prebreakfast (we assumed a time of 0700), postbreakfast (0830), prelunch (1200), postlunch (0130), presupper (1800), postsupper (1930), and bedtime (2200) on 24,652 occasions. An additional data point was collected at 0300, but since this was only measured in <1% of subjects, it is not considered further. Mean blood glucose was calculated by the area under the curve (AUC) using the trapezoidal rule in accordance with Rohlfing et al. (14). Instability of blood glucose (within-day SD) was calculated as the SD of daily blood glucose around the mean from each quarterly visit (15). Variability in MBG over time was estimated as the SD of the MBG (AUC) measurements measured at each quarter. Mean preprandial glucose was taken as the average of prebreakfast, prelunch, and presupper and mean postprandial glucose as the average of postbreakfast, postlunch, and postsupper.

The relationship between each risk factor and the development of diabetes complications was assessed by Cox regression from which hazard ratios (HRs) and 95% CIs were calculated. The Cox regression model is semiparametric in the sense that no assumption concerning event-free survival times is necessary. The Cox regression model is based on the assumption that the effect of a risk factor, expressed as an HR, is constant over time. The assumption of proportionality of the Cox model covariates was tested by plotting Schoenfeld residuals (16,17). We also fitted a separate Cox model for MBG (AUC) assuming that MBG was a segmented time-dependent covariate within the Cox model structure. This model takes into account the different measurements for MBG over time. MBG was measured at quarterly intervals throughout the study period. In the segmented time-dependent model, if MBG was measured at more than baseline but less than the first quarter, the baseline value is used. If MBG was measured at more than the first quarter but less than the second, the value at first quarter is used and so on. Hence, the mean is continuously updated. All Cox regression models were adjusted for the following baseline covariates: age (years), sex, disease duration (years), randomization treatment (conventional versus intensive), prevention cohort (primary versus secondary), and study phase (first or second). The GLIM4 and SPSS statistical computer packages were used to analyze the data. An arbitrary level of 5% statistical significance (two tailed) was assumed.

RESULTS — A residual plot for mean MBG (AUC) versus survival time showed the residuals centered around zero, indicating no departure from proportionality of hazards. Univariate Cox regression models are presented in Table 1. Using the MBG profile, larger HRs were seen with retinopathy (1.16) as an outcome measure when compared with nephropathy (1.04). For the time-dependent model, the HRs were similar for both complications (retinopathy 1.12, nephropathy 1.07). Given similar estimates

Table 2—*Multivariate Cox regression models relating glycemia to microvascular complications*

Variable	Nephropathy	*P* value	Retinopathy	*P* value
Model 1				
MBG (AUC)	1.03 (0.96–1.11)	0.42	1.15 (1.06–1.25)	<0.0001
SD MBG (AUC)	0.96 (0.82–1.11)	0.57	0.97 (0.81–1.16)	0.72
SD (within day)	1.01 (0.99–1.03)	0.32	1.02 (0.99–1.04)	0.18
Model 2				
Preprandial	1.08 (0.94–1.24)	0.28	1.11 (0.95–1.30)	0.18
Postprandial	0.99 (0.89–1.12)	0.83	1.08 (0.94–1.24)	0.31

Data are HR (95% CI). Both models adjusted for baseline covariates. MBG (AUC), AUC of seven-point blood glucose profile (mmol/l); SD MBG (AUC), SD of between-visit AUC; SD (within-day), SD of glucose profile.

of effect size and residual plots showing no departure from proportionality, the rest of our Cox models did not assume a time-dependent relationship. Two multivariable Cox models are presented in Table 2. Complication risk was not significantly related to variability in blood glucose after adjusting for MBG (AUC) (model 1, Table 2). Figure 1 shows the relative contribution of rises in both MBG and within-day glucose variability to retinopathy risk as derived from the multivariate model. Considering both pre- and postprandial MBG together in the same Cox regression model, neither was significantly associated with complication outcome (model 2, Table 2).

There was a nonsignificant ($P = 0.09$) trend to less within-day variability among patients using an insulin pump 99–100% of the time (average within-day SD 2.75 mmol/l) compared with intermittent users (3.00 mmol/l) and those only taking multiple injections (3.11 mmol/l).

CONCLUSIONS — This study has shown that the variability in blood glucose around a patient's mean value has no influence on the development or progression of either retinopathy or nephropathy in type 1 diabetes. Thus, on average, one patient with wildly fluctuant glucose concentrations is likely to have the same risk of these complications as one whose glycemia varies little throughout the day, so long as their mean (AUC) glucose values remain similar. We have also found that neither pre- nor postprandial glucose concentrations preferentially contribute to the risk of microvascular disease.

There are few studies other than the DCCT that have been able to directly relate glycemia to microvascular complication risk. Although the U.K. Prospective Diabetes Study showed similar findings in a group with type 2 diabetes (4), only fasting glucose measurements were recorded and not the detailed profiles found here. However, by comparing patients on insulin with those on oral agents, the U.K. Prospective Diabetes Study probably unwittingly gave an insight into the effect of glucose variability on complication risk. As neither of these groups appeared at a risk any different to that expected for their A1C, the relative glycemic instability of patients on insulin did not seem to confer a higher probability of microvascular disease. Our findings are also consistent with a recent study using DCCT data that found that glycemic instability had little influence on the A1C value of a patient (8).

Notwithstanding, it has certainly been proposed that the reason conventionally treated patients in the DCCT were at apparently higher chance of developing retinopathy at any given A1C value than those treated intensively is because of their relatively greater glycemic instability (3). A similar explanation has been given for the reduction in complications seen in adolescents with type 1 diabetes between 1990 and 2002 (6). By showing in the current study that glucose variability does not influence the relationship between AUC glucose and retinopathy, it would suggest that there must be other reasons for these findings, which may or may not be related to the glycemia of the patients involved. With particular regard to the DCCT, our data analysis has also shown that the lack of influence of glycemic stability is independent of whether the patient was in the conventional or intensive treatment group.

Postprandial glucose measurements are only one component of the variability in blood glucose within an individual but have received considerable attention as a predictor of cardiovascular disease, especially in subjects not already known to have diabetes (18–23). The role of postprandial glucose in the development of microvascular complications is less well established and has seldom extended beyond assuming reductions in risk on the basis of changes in A1C (24–26). Recently, a cross-sectional study of subjects with type 2 diabetes, but not insulin treated, has suggested that postprandial glucose may be a better predictor of retinopathy (though not nephropathy or neuropathy) in this group of patients (27,28). In contrast, our data analysis has found that while both pre- and postprandial glucose measurements are individually predictive of retinopathy in a univariate analysis, there is no evidence that either measurement is superior to the other in establishing risk in the DCCT group of patients.

The fact that MBG was predictive of retinopathy in both univariate and multivariate analysis, while it was a relatively poor predictor of microalbuminuria progression, is likely to be partly a consequence of the degree of random within-patient variability in this latter measurement (29). It is also possible that MBG is actually a poorer predictor of this complication than A1C measurement.

The weight that can be placed on the findings of this study directly relate to the strengths inherent in the DCCT database due to its size and the rigor of its protocol. This is reflected in the large ($n = 24,652$) number of seven-point glucose profiles collected. These were performed every 3 months during the study, were from samples collected throughout most of the day (including both pre- and postprandially), and were then analyzed by a laboratory. Crucially, the study was also benefited by being performed before other potential confounding factors such as antihypertensives and lipid-lowering agents came in to common use.

These findings are of direct relevance to the clinical management of patients with type 1 diabetes. Patients with the greatest variability in blood glucose are often those most likely to face quality-of-life issues related to hypo- and hyperglycemia (30). It is therefore natural to consider that they could be at especially high risk of the microvascular complications of diabetes as well. However, this study would indicate that these individuals, and their caring physicians, can be reassured that they are at no greater risk of retinopathy than their glucose AUC suggests.

This study also gives guidance to pa-

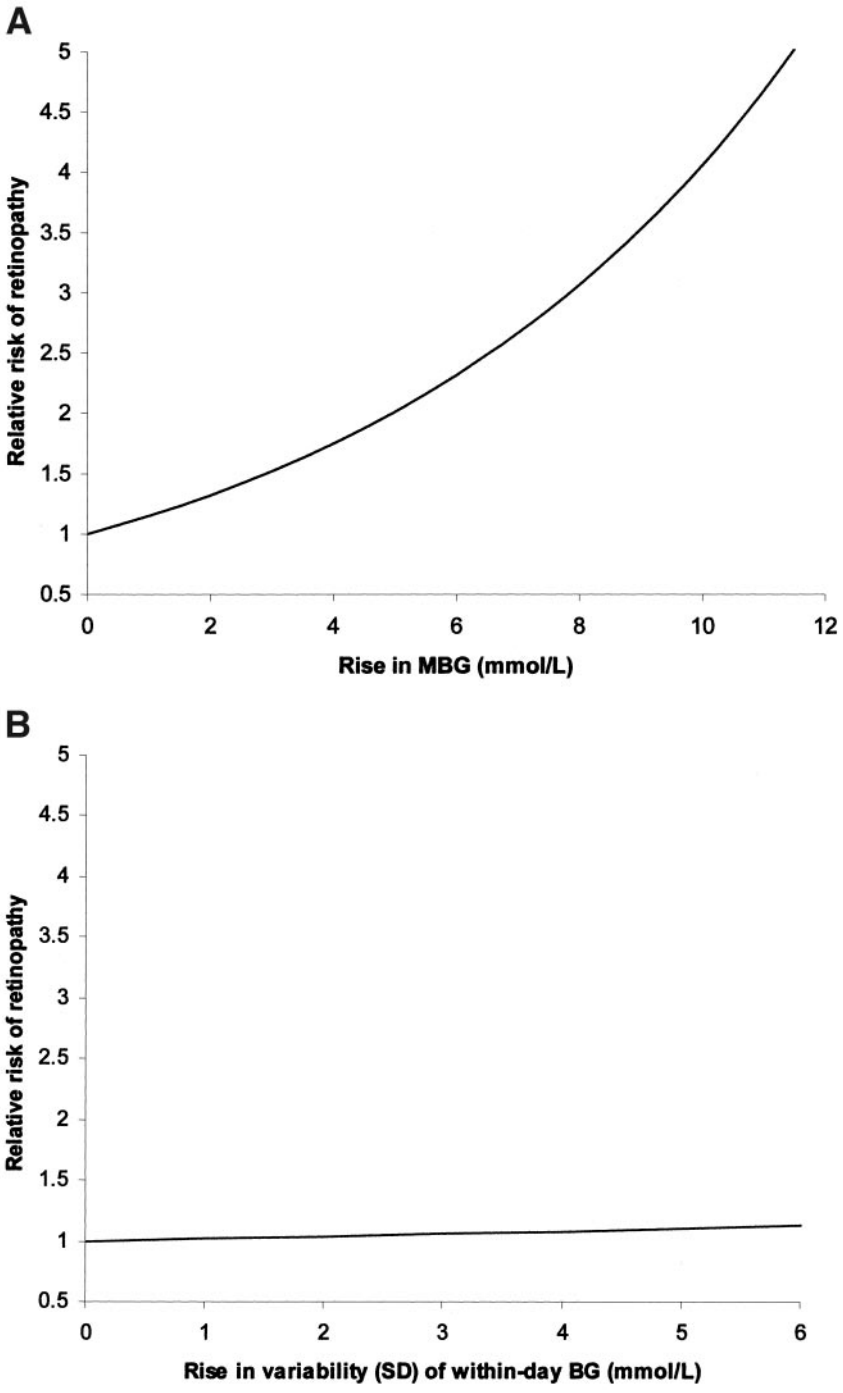

Figure 1—*Relative risk of retinopathy as a function of increasing MBG (*$P < 0.0001$*) (*A*) and increasing variability (SD) (*B*) of the within-day blood glucose profile (NS).*

tients who self-monitor their blood glucose. Current recommendations do not stipulate a need to measure postprandial blood glucose in preference to basal values (31), and the data presented here suggest that there is no specific need for this to change in order to reduce the likelihood of small-vessel complications. As treatments move toward the increasing use of analog insulins with both long- and short-term modes of action (30), these data also infer that no preference in targeting either pre- or postprandial glucose is required if the aim is purely to reduce microvascular risk.

In summary, this study has shown that pre- and postprandial glucose values are equally predictive of the microvascular complications of type 1 diabetes and that blood glucose variability does not appear to be an additional factor in their development.

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