Effect of Glucose Variability on the Long-Term Risk of Microvascular Complications in Type 1 Diabetes

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OBJECTIVE — This study analyzed data from the Epidemiology of Diabetes Interventions and Complications (EDIC) study to see whether longer-term follow-up of Diabetes Control and Complications Trial (DCCT) patients reveals a role for glycemic instability in the development of microvascular complications.

RESEARCH DESIGN AND METHODS — The mean area under the curve glucose and the within-day glucose variability (SD and mean amplitude of glycemic excursions [MAGE]) during the DCCT were assessed to see whether they contributed to the risk of retinopathy and nephropathy by year 4 of the EDIC.

RESULTS — Logistic regression analysis showed that mean glucose during the DCCT and mean A1C during EDIC were independently predictive of retinopathy (each $P < 0.001$) as well as A1C during EDIC of nephropathy ($P = 0.001$) development by EDIC year 4. Glucose variability did not add to this (all $P > 0.25$ using SD or MAGE).

CONCLUSIONS — Glucose variability in the DCCT did not predict the development of retinopathy or nephropathy by EDIC year 4.

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Analysis of the Diabetes Control and Complications Trial (DCCT) dataset has shown that glucose variability did not appear to be a further factor in the development or progression of either retinopathy or nephropathy (1,2). More recently, variability in A1C, a longer-term marker of glycemic control, during the DCCT has been found to add to the risk already indicated by the mean A1C value (3).

This current study has examined data from the first 4 years of the DCCT extension study, the Epidemiology of Diabetes Interventions and Complications (EDIC) study. The EDIC has already shown the long-term beneficial effects of intensive treatment on microvascular complications (4–6). Our goal was to establish whether the follow-up study also unearths a longer-term relationship between glucose variability during the DCCT and subsequent retinopathy and nephropathy.

RESEARCH DESIGN AND METHODS

— We used the publicly accessible datasets stored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) relating to both the DCCT and the first 4 years of the EDIC study. After an average period of 6.5 years enrollment in the DCCT, patients were offered intensive glucose management and were asked to continue with follow-up as part of the EDIC study (7).

Retinopathy development and progression was defined as a ≥3-unit change in the 25-point Early Treatment Diabetic Retinopathy Study (ETDRS) score measured at baseline and in all patients completing year 4 in the EDIC ($n = 1,208$), as well as in a subset of patients at years 1 ($n = 369$), 2 ($n = 447$), and 3 ($n = 419$). Nephropathy was defined as an albumin excretion rate >40 mg/day.

A seven-point blood glucose profile was requested to be taken throughout the day at three monthly intervals during, but not beyond, the DCCT. Mean blood glucose (area under the curve) and glucose variability (SD and mean amplitude of glycemic excursions [MAGE] [8]) during the DCCT were calculated as published previously (9). Results were virtually identical for the blood glucose profiles based on five or more readings and are not considered further.

Statistical methods

We used the generalized estimating equation with a logit link to assess the effect of covariates on the odds of development or progression of retinopathy and nephropathy over repeated time points (10,11) using the Stata statistical computer package (12). Wald robust estimates of SE were used to estimate 95% CIs. The two treatment groups (intensive versus conventional) were analyzed separately and combined. Models were adjusted as described in Table 1.

RESULTS

— Patients with a three-step or more change in the ETDRS at years 1, 2, 3, and 4 were 15 of 369 (4%), 37 of 443 (8%), 47 of 419 (11%), and 146 of 1,208 (12%), respectively. A total of 115 of 1,343 (9%) patients had an ETDRS score ≥3 at EDIC baseline. Patients with nephropathy (albumin excretion rate >40 mg/day) at years 3 and 4 were 184 of 1,302 (14%). The mean ± SD variability of glucose was 4.11 ± 0.88 and 8.01 ± 2.00 mmol/l for SD and MAGE, respectively.

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Table 1—*Longitudinal multiple logistic regression models for microvascular complications*

	Intensive		Conventional		Combined	
	Odds ratio (95% CI)	*P*	Odds ratio (95% CI)	*P*	Odds ratio (95% CI)	*P*
Retinopathy						
Model 1						
A1C eligibility, DCCT	0.94 (0.76–1.16)	0.59	1.04 (0.90–1.21)	0.52	1.02 (0.90–1.15)	0.73
Mean BG, DCCT	1.31 (0.96–1.77)	0.08	1.32 (1.19–1.46)	<0.001	1.31 (1.19–10.44)	<0.001
MAGE, DCCT	1.03 (0.82–1.29)	0.27	0.92 (0.83–1.02)	0.15	0.96 (0.88–1.05)	0.45
Mean A1C, EDIC	1.66 (1.31–2.150)	<0.001	1.29 (1.08–1.54)	0.004	1.41 (1.22–1.62)	<0.001
Model 2						
A1C eligibility, DCCT	0.94 (0.76–1.16)	0.59	1.04 (0.90–1.201)	0.5	1.02 (0.90–1.15)	0.11
Mean BG, DCCT	1.26 (0.90–1.76)	0.16	1.35 (1.21–1.49)	<0.001	1.33 (1.21–1.51)	<0.001
SDBG, DCCT	1.16 (0.69–1.93)	0.55	0.82 (0.65–1.03)	0.09	0.9 (0.74–1.10)	0.32
Mean A1C, EDIC	1.66 (1.31–2.11)	<0.001	1.26 (1.06–1.51)	0.008	1.39 (1.20–1.60)	<0.001
Nephropathy						
Model 1						
A1C eligibility, DCCT	1.31 (0.97–1.76)	0.07	1.35 (1.07–1.71)	0.011	1.33 (1.09–1.610)	0.003
Mean BG, DCCT	0.97 (0.62–1.52)	0.9	1.08 (0.93–1.26)	0.29	1.08 (0.93–1.24)	0.29
MAGE, DCCT	1.13 (0.90–1.43)	0.26	0.99 (0.86–1.15)	0.96	1.01 (0.89–1.14)	0.8
Mean A1C, EDIC	1.46 (1.11–1.91)	0.005	1.34 (1.02–1.76)	0.03	1.38 (1.13–1.67)	0.001
Model 2						
A1C eligibility, DCCT	1.29 (0.96–1.73)	0.08	1.36 (1.07–1.71)	0.01	1.32 (1.09–1.60)	0.003
Mean BG, DCCT	1.08 (0.65–1.78)	0.75	1.1 (0.95–1.28)	0.17	1.11 (0.96–1.28)	0.14
SDBG, DCCT	0.99 (0.54–1.83)	0.99	0.83 (0.59–1.18)	0.31	0.86 (0.64–1.15)	0.31
Mean A1C, EDIC	1.44 (1.11–1.86)	0.005	1.33 (1.01–1.76)	0.037	1.38 (1.13–1.67)	0.001

Models adjusted for age (EDIC baseline), disease duration (EDIC baseline), and sex. Retinopathy models further adjusted for laser therapy in DCCT, and nephropathy further adjusted for patients with microalbuminuria at the DCCT closeout. Example interpretation: A1C odds ratio represents proportionate change per 1% unit difference in A1C. BG, blood glucose; SDBG, SD of blood glucose.

There was no significant relationship between blood glucose variability in the DCCT and the development or progression of retinopathy in EDIC after adjustment (Table 1). Associations between nephropathy and glycemia were generally less strong than those for retinopathy, with the exception of A1C at eligibility. Our focus has been on new events since the end of the DCCT. A separate analysis taking any event, irrespective of the time of event, from the DCCT up to and including the EDIC showed that there was no significant relationship with blood glucose variability (data not shown).

CONCLUSIONS — This analysis has extended the follow-up of DCCT patients to year 4 of the EDIC study and found no evidence, or even a signal, that this uncovers a role for glucose variability in adding to the risk of retinopathy and nephropathy already predicted by the mean glucose alone.

This finding is consistent with two analyses of events in the DCCT alone, which seemingly showed glucose variability to be of little relevance to complication risk (1,2). However, variations in A1C (as opposed to glucose) around a mean A1C value do indeed seem to predict small vessel complications, raising the possibility either that long-term fluctuations in glycemia are more important than short-term ones or that A1C was more sensitive in detecting glycemic variability than the method used to assess mean glucose in the DCCT (3). An additional observation is that A1C at the start of the DCCT, which was a strong predictor of retinopathy during the DCCT, was not such a good predictor in this analysis of EDIC. This may be an earlier indication of the waning effect of metabolic memory described recently in respect to the legacy effect that A1C during the DCCT had on retinopathy by year 10 of EDIC (13).

There are limitations to this study, with the most important being the lack of glucose profiling during EDIC and the inability to precisely evaluate diurnal glycemic variation from quarterly seven-point glucose profiles. Regarding the first limitation, we determined this analysis should regard glucose variability during the DCCT as one of the baseline covariates at the start of EDIC. With respect to glycemic control throughout EDIC, we have also accounted for A1C during the extension study, and it is reassuring that all patients were offered the same intensive treatment during this period. Counterbalancing any limitations are the size of the DCCT/EDIC dataset (e.g., there was more than 22,000 seven-point glucose profiles during the DCCT) and the fact that the study is, in many respects, impossible to reproduce because it was performed in an era when possible confounding factors, such as the use of antihypertensive, antiplatelet, and lipid-lowering agents, were not in routine use.

In summary, increasing the follow-up period of DCCT patients to year 4 of EDIC has not unearthed an association between glucose variability and microvascular complication risk that adds to that already predicted by a patient's mean glucose value.

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