The 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 Epidemiology of Diabetes Interventions and Complications (EDIC) study to see if 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 (AUC) glucose and the within-day glucose variability (SD and MAGE) during the DCCT was assessed to see how they contributed to the risk of retinopathy and nephropathy by year 4 of EDIC.

Results: Logistic regression showed that the mean glucose during the DCCT and mean HbA$_{1c}$ during EDIC were independently predictive of retinopathy (each p<0.001) and EDIC HbA$_{1c}$ of nephropathy (p=0.001) development by EDIC year 4, whereas 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.
Analysis of the Diabetes Control and Complications (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). However, more recently, variability in HbA1c, a longer term marker of glycemic control, during the DCCT has indeed been found to add to the risk already indicated by the mean HbA1c value (3).

This current study has examined data from the first 4 years of the DCCT extension study, the Epidemiology of Diabetes Intervention and Complications (EDIC) study. EDIC has already shown the long-term beneficial effects of intensive treatment on microvascular complications (4-6). We wished to establish the follow-up study might also unearth a longer term relationship between glucose variability during the DCCT and subsequent retinopathy and nephropathy.

**RESEARCH DESIGN AND METHODS**

**The datasets:** 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 EDIC study. After an average period of 6.5 years in the DCCT, all were offered intensive glucose management and were asked to continue to be followed up as part of the EDIC study (7).

**Definition of events:** Retinopathy development and progression was defined as a ≥ 3 unit change in the 25-point Early Diabetes Retinopathy Treatment Study (EDTRS) score measured at baseline and in all patients completing year 4 in EDIC (n=1208), 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 AER > 40 mg/day.

**Glycemic variables:** A 7 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 (as an area under the curve) and glucose variability (as SD and MAGE statistic (8)) during the DCCT was calculated as published elsewhere (9). Results were virtually identical for the BG profiles based on 5 or more readings and are not considered further.

**Statistical methods:** We used the generalized estimating equation (GEE) with a logit link to assess the effect of covariates on the odds of the development or progression of retinopathy and nephropathy over repeated time-points (10; 11) using the Stata statistical computer package (12). Ninety five percent confidence intervals were estimated using Wald robust estimates of the standard error.

The two treatment groups (intensive versus conventional) were analysed separately and combined. Models were adjusted as described in table 1.

**RESULTS**

The numbers (%) of patients with a three-step or more change in the EDTRS at years 1, 2, 3 and 4 was 15/369 (4%), 37/443 (8%), 47/419 (11%) and 146/1208 (12%) respectively. A total of 115/1343 (9%) patients had an EDTRS score of 3 or more at EDIC baseline. The number of patients with nephropathy (AER > 40 mg/day) at years 3 and 4 was 184/1302 (14%). The mean±SD variability of glucose was 4.11±0.88mmol/L and 8.01±2.00mmol/L for standard deviation and MAGE respectively.

**Retinopathy and nephropathy:** There was no significant relationship between BG 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 HbA1c 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 an
including EDIC showed that there was no
significant relationship with BG variability
(data not shown).

DISCUSSION
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 looking at events in just the DCCT,
which seemingly showed glucose variability
to be of little relevance to complication risk
(1; 2). However, variations in HbA1c (as
opposed to glucose) around a mean HbA1c
value do indeed seem to predict small vessel
complications raising the possibility that
either long-term fluctuations in glycemia are
more important than short-term ones, or that
HbA1c was more sensitive in detecting
glycemic variability than the method
employed to assess mean glucose in the
DCCT (3).

An additional observation is that
HbA1c 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 of the
legacy effect that HbA1c during the DCCT
had on retinopathy by year 10 of EDIC (13).

There are limitations to this study, the
most important being the lack of glucose
profiling during EDIC and the inability to
precisely evaluate diurnal glycemic variation
from quarterly 7 point glucose profiles.
Regarding the first limitation, we made the
decision that this analysis should regard
glucose variability during the DCCT as one of
the baseline co-variates at the start of EDIC.

With respect to glycemic control throughout
EDIC we have also taken account of HbA1c
during the extension study and it is reassuring
that all patients were offered the same
intensive treatment during this period.
Counterbalancing any limitations is the size
of the DCCT/EDIC dataset (for example,
there was in excess of 22 thousand seven-
point glucose profiles during the DCCT) and
the way in which 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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Interventions and Complications (EDIC)
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the General Clinical Research Center
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prepared under the auspices of the
DCCT/EDIC study and does not represent
analyses nor conclusions of the DCCT/EDIC
study group nor the NIH.

We wish to thank the DCCT/EDIC
investigators for making their trial dataset
public and therefore allowing independent
investigators to analyse their work for the
benefit of patients with type 1 diabetes.
REFERENCES
Table 1. Longitudinal multiple logistic regression models for microvascular complications

<table>
<thead>
<tr>
<th></th>
<th>Intensive OR (95% CI)</th>
<th>Model 1</th>
<th>Conventional OR (95% CI)</th>
<th>Model 2</th>
<th>Combined OR (95% CI)</th>
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<tr>
<td>HbA1c eligibility DCCT</td>
<td>0.94 (0.76,1.16)</td>
<td>0.59</td>
<td>1.04 (0.90,1.21)</td>
<td>0.52</td>
<td>1.02 (0.90,1.15)</td>
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<tr>
<td>Mean BG DCCT</td>
<td>1.31 (0.96,1.77)</td>
<td>0.08</td>
<td>1.32 (1.19,1.46)</td>
<td>&lt;0.001</td>
<td>1.31 (1.19,1.44)</td>
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<td>MAGE DCCT</td>
<td>1.03 (0.82,1.29)</td>
<td>0.27</td>
<td>0.92 (0.83,1.02)</td>
<td>0.15</td>
<td>0.96 (0.88,1.05)</td>
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<td>HbA1c mean EDIC</td>
<td>1.66 (1.31,2.150)</td>
<td>&lt;0.001</td>
<td>1.29 (1.08,1.54)</td>
<td>0.004</td>
<td>1.41 (1.22,1.62)</td>
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<td>1.04 (0.90,1.201)</td>
<td>0.5</td>
<td>1.02 (0.90,1.15)</td>
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<tr>
<td>Mean BG DCCT</td>
<td>1.26 (0.90,1.76)</td>
<td>0.16</td>
<td>1.35 (1.21,1.49)</td>
<td>&lt;0.001</td>
<td>1.33 (1.21,1.51)</td>
<td>&lt;0.001</td>
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<tr>
<td>SDBG DCCT</td>
<td>1.16 (0.69,1.93)</td>
<td>0.55</td>
<td>0.82 (0.65,1.03)</td>
<td>0.09</td>
<td>0.9 (0.74,1.10)</td>
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<td>HbA1c mean EDIC</td>
<td>1.66 (1.31,2.11)</td>
<td>&lt;0.001</td>
<td>1.26 (1.06,1.51)</td>
<td>0.008</td>
<td>1.39 (1.20,1.60)</td>
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<td><strong>Nephropathy</strong></td>
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<tr>
<td>HbA1c eligibility DCCT</td>
<td>1.31 (0.97,1.76)</td>
<td>0.07</td>
<td>1.35 (1.07,1.71)</td>
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<td>1.33 (1.09,1.610)</td>
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<td>Mean BG DCCT</td>
<td>0.97 (0.62,1.52)</td>
<td>0.9</td>
<td>1.08 (0.93,1.26)</td>
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<td>1.08 (0.93,1.24)</td>
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<td>MAGE DCCT</td>
<td>1.13 (0.90,1.43)</td>
<td>0.26</td>
<td>0.99 (0.86,1.15)</td>
<td>0.96</td>
<td>1.01 (0.89,1.14)</td>
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<td>HbA1c mean EDIC</td>
<td>1.46 (1.11,1.91)</td>
<td>0.005</td>
<td>1.34 (1.02,1.76)</td>
<td>0.03</td>
<td>1.38 (1.13,1.67)</td>
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<td>Model 2</td>
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<tr>
<td>Mean BG DCCT</td>
<td>1.08 (0.65,1.78)</td>
<td>0.75</td>
<td>1.1 (0.95,1.28)</td>
<td>0.17</td>
<td>1.11 (0.96,1.28)</td>
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<tr>
<td>SDBG DCCT</td>
<td>0.99 (0.54,1.83)</td>
<td>0.99</td>
<td>0.83 (0.59,1.18)</td>
<td>0.31</td>
<td>0.86 (0.64,1.15)</td>
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<tr>
<td>HbA1c mean EDIC</td>
<td>1.44 (1.11,1.86)</td>
<td>0.005</td>
<td>1.33 (1.01,1.76)</td>
<td>0.037</td>
<td>1.38 (1.13,1.67)</td>
<td>0.001</td>
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</table>

Models adjusted for age (EDIC baseline), disease duration (EDIC baseline) and gender. Retinopathy models further adjusted for laser therapy in DCCT and nephropathy further adjusted for patients with microalbuminuria at DCCT closeout.

Example interpretation: HbA1c odds represents proportionate change per 1% unit difference in HbA1c