What goes up must come down: glucose variability and glucose control in diabetes and critical illness
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Chapter 6

Glucose variability does not contribute to the development of peripheral and autonomic neuropathy in type 1 diabetes: data from the DCCT

Sarah E. Siegelaar, Eric S. Kilpatrick, Alan S. Rigby, Steven L. Atkin, Joost B.L. Hoekstra and J. Hans DeVries

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Abstract

Aims/hypothesis: While the presence of an effect of glycaemic variability on retinopathy and nephropathy has been negated, it is unknown whether glycaemic variability may influence neuropathy. We analysed data from the Diabetes Control and Complications Trial (DCCT) dataset to assess whether glycaemic variability is a risk factor for the development of diabetic neuropathy.

Methods: Seven-point glucose profiles were collected quarterly during the DCCT in 1,441 type 1 diabetes patients. Peripheral and autonomic neuropathies were assessed at baseline and at 5 and 4 years follow-up, respectively. The effect of glycaemic variability, expressed as standard deviation (SD) and mean amplitude of glycaemic excursions (MAGE), on the development of neuropathy in addition to HbA1c and mean glucose was assessed using a logistic regression model, adjusted for age, sex, disease duration, treatment group and prevention cohort.

Results: Glucose variability had no significant effect on the incidence of clinical neuropathy confirmed by autonomic or electromyography abnormalities (SD, odds ratio [OR] 1.07, 95% confidence interval [CI] 0.83-1.35; MAGE, 1.06 [0.96-1.20]) or clinical neuropathy alone (SD, 0.95 [0.77-1.18]; MAGE, 1.01 [0.91-1.11]). It appeared to have a significant effect on overall autonomic dysfunction but not when adjusting for HbA1c or mean glucose (SD, OR 1.08 and 1.09, CI 0.82-1.44 and 0.80-1.48, respectively; MAGE, OR 1.09 and 1.10, CI 0.96-1.23 and 0.97-1.25 respectively).

Conclusions: Glucose variability was not an additional risk factor in the development of diabetic peripheral or autonomic neuropathy over and above HbA1c or mean glucose in the DCCT.
Introduction

Diabetes is one of the most common causes of small fibre neuropathy causing sensory symptoms as pain and numbness as well as autonomic dysfunction. Large fibre involvement is frequent, which makes neuropathy an important complication of diabetes, potentially leading to disability and premature deaths. It is thought that hyperglycaemia causes direct damage to the nerve parenchyma as well as indirect hyperglycaemia-induced neuronal ischemia by decreases in neuronal flow. Good glycaemic control is a proven robust measure to delay or prevent the development of diabetic polyneuropathy. Other cardiovascular risk-factors such as body mass index and hypertension are associated with this complication in type 1 diabetes and are therefore assessed in prevention programmes.

It is suggested that, in addition to hyperglycaemia, glucose variability can contribute to the severity and development of diabetic neuropathy because the nervous system may be particularly susceptible to glycaemic fluctuations. On the other hand, glucose variability is not related to the development of retinopathy and nephropathy in type 1 diabetes. To determine any additional effect of glucose variability, above that assessed by HbA1c and mean glucose, on peripheral and autonomic diabetic neuropathy, we analyzed the data from the Diabetes Control and Complications Trial (DCCT).

Methods

The datasets
We used for this study the datasets collected during the DCCT (publicly accessible at, www.gcrc.med.umn.edu/gcrc/downloads/dcct.html, accessed 23-27 January 2009). The DCCT was a 9-year follow-up study of 1,441 patients with type 1 diabetes comparing the effects of intensive versus conventional treatment on the development of microvascular complications and neuropathy. A standardised neurologic history, physical examination and nerve conduction studies were done by DCCT neurologists at baseline, 5 years, and study end. Autonomic nervous system tests were performed at baseline and biennially thereafter. We included only data from baseline to 4 years (autonomic function data) or 5 years of follow-up in the analyses as more than 50% of the patients did not have records of glucose data after 5 years of follow-up.

Definition of events
Clinical neuropathy was defined as abnormal findings in two or more of the following categories in the absence of other known causes of neuropathy: neuropathic symptoms (dysesthesias, paresthesias, hypersensitivity to touch and burning pain), sensory deficits
(light touch, position, temperature and pin-prick) or deep tendon reflexes. The nerve conduction studies consisted of median motor and sensory, peroneal motor and sural sensory nerve conduction velocities; distal latencies and amplitudes; and median and peroneal motor F-wave latencies using a standard protocol. Abnormal nerve conduction was considered present when at least one measured attribute was abnormal in at least two anatomically distinct nerves. Autonomic nervous system function was assessed using three tests: beat-to-beat heart rate variation (R-R variation) during deep breathing and during a standardised Valsalva maneuver, and postural blood pressure testing. Abnormal autonomic function was determined as at least one abnormal autonomic function test. The main neurological endpoint of the DCCT was the development of confirmed clinical neuropathy, defined as clinical neuropathy confirmed by either abnormal nerve conduction or autonomic nervous system testing.

We studied the effect of glucose variability on the main neurological endpoint, i.e. confirmed clinical neuropathy, and on the DCCT-defined secondary endpoints separately: clinical neuropathy, abnormal nerve conduction studies, and abnormal autonomic function. In addition, we determined its effect on the subvariables median motor F-wave latency, sural amplitude, sensory signs, and beat-to-beat heart-rate variation (with Valsalva ratio <1.5), as these variables tend to be the first affected by diabetes.

Glycaemic variables
During the DCCT a seven-point blood glucose profile was collected every 3 months (pre breakfast, post breakfast, pre lunch, post lunch, pre supper, post supper and bedtime). An additional data point was collected during the night, but since this was only measured in <1% of the subjects, it is left out of further analysis. We included all profiles with five observations or more during the 24-hr period, extrapolating missing values from the surrounding points. Mean blood glucose was calculated by the area under the curve (AUC) using the trapezoidal rule. Variability of blood glucose was calculated as the SD of daily blood glucose around the mean from each quarterly visit (within-day SD) and the mean amplitude of glycaemic excursions (MAGE). Last, we calculated the mean SD from individual glucose data transformed to a symmetric distribution according to Kovatchev. Glucose variability from baseline to 4 or 5 years was assessed as the mean SD and mean MAGE from the first quarter till the 16th or 20th quarter of follow-up, respectively.

Statistical analysis
The relationship between glucose variability and the development of each diabetic neuropathy variable was assessed by a logistic regression model from which odds ratios (OR) and 95% confidence intervals (CI) were calculated. Patients with a positive baseline score on the neuropathy parameter studied were excluded from analysis. All regression models were adjusted for the following baseline covariates: age (years), sex, disease
duration (years), randomization treatment (conventional vs. intensive) and prevention cohort (primary vs. secondary). Finally, the additional effect of glucose variability on neuropathy separate from the effect of HbA1c and mean glucose (AUC) was computed using the same technique. Statistical analysis was performed using SPSS version 16.0.2. A P-value <0.05 was considered significant.

Results

The main characteristics of the patients in the group analysed for confirmed clinical neuropathy are listed in Table 1. Of the 1,441 patients in total, 1,160 were included in this specific analysis. Ninety-two patients were excluded from the analysis because they had a positive score at baseline, and 189 patients had missing data on confirmed clinical neuropathy at baseline (n = 3) or at 5 years (n = 186). The numbers of participants with data analysed in the other specific neuropathy groups are listed in Table 2.

Table 1 Patient characteristics in the group analysed for confirmed clinical neuropathy

<table>
<thead>
<tr>
<th>Confirmed clinical neuropathy</th>
<th>Yes (n = 108)</th>
<th>No (n = 1052)</th>
<th>P - value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at baseline, years</td>
<td>28.28 (6.77)</td>
<td>26.40 (7.10)</td>
<td>0.008</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>52 (48)</td>
<td>533 (53)</td>
<td>0.38</td>
</tr>
<tr>
<td>Diabetes duration at baseline, months</td>
<td>79.59 (45.62)</td>
<td>68.60 (49.79)</td>
<td>0.02</td>
</tr>
<tr>
<td>Conventional treatment, n (%)</td>
<td>80 (74)</td>
<td>517 (49)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Primary prevention cohort, n (%)</td>
<td>35 (32)</td>
<td>503 (48)</td>
<td>0.002</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>9.10 (1.58)</td>
<td>8.08 (1.43)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean glucose, mmol/l</td>
<td>13.51 (3.33)</td>
<td>11.52 (3.78)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MAGE, mmol/l</td>
<td>8.00 (1.96)</td>
<td>7.55 (1.90)</td>
<td>0.02</td>
</tr>
<tr>
<td>SD, mmol/l</td>
<td>4.24 (0.89)</td>
<td>4.05 (0.93)</td>
<td>0.04</td>
</tr>
<tr>
<td>SD TF, mmol/l</td>
<td>0.75 (0.17)</td>
<td>0.81 (0.16)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are means (SD), unless stated otherwise in parentheses. For this analysis patients with a positive or missing score for confirmed clinical neuropathy at baseline were excluded (neuropathy, n = 92; missing, n = 3). Patients with a missing score at 5 years are also excluded from the analysis (n = 186). P-values are comparisons between groups (independent samples t-test). MAGE, mean amplitude of glycaemic excursions; SD, standard deviation; SD TF, standard deviation obtained from glucose data transformed according to Kovatchev et al.: transformed blood glucose = 1.794*(log(BG)^1.026 - 1.861)^14.
Table 2 Binary logistic regression analysis relating the effect of different glycaemic variables to neurological complications, as defined by the DCCT

<table>
<thead>
<tr>
<th>model</th>
<th>Confirmed clinical neuropathy (a)</th>
<th>Clinical neuropathy (a)</th>
<th>Autonomic neuropathy (b)</th>
<th>Abnormal nerve conduction (a)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 108/1160^c)</td>
<td>(n = 148/1113^c)</td>
<td>(n = 79/1258^c)</td>
<td>(n = 207/813^c)</td>
</tr>
<tr>
<td>HbA1c</td>
<td>1.64 (1.37-1.95) (&lt;0.001)</td>
<td>1.40 (1.20-1.64) (&lt;0.001)</td>
<td>1.51 (1.23-1.85) (&lt;0.001)</td>
<td>1.62 (1.39-1.90) (&lt;0.001)</td>
</tr>
<tr>
<td>AUC</td>
<td>1.17 (1.09-1.26) (&lt;0.001)</td>
<td>1.13 (1.05-1.21) (0.001)</td>
<td>1.15 (1.05-1.26) (0.003)</td>
<td>1.15 (1.07-1.23) (&lt;0.001)</td>
</tr>
<tr>
<td>SD</td>
<td>1.07 (0.83-1.35) (0.67)</td>
<td>0.95 (0.77-1.18) (0.66)</td>
<td>1.30 (0.99-1.70) (0.06)</td>
<td>1.17 (0.96-1.42) (0.12)</td>
</tr>
<tr>
<td>SD (HbA1c)</td>
<td>0.86 (0.67-1.10) (0.24)</td>
<td>0.82 (0.66-1.03) (0.08)</td>
<td>1.08 (0.82-1.44) (0.58)</td>
<td>0.94 (0.75-1.14) (0.46)</td>
</tr>
<tr>
<td>SD (AUC)</td>
<td>0.85 (0.65-1.10) (0.21)</td>
<td>0.78 (0.61-0.99) (0.04)</td>
<td>1.09 (0.80-1.48) (0.59)</td>
<td>0.95 (0.76-1.19) (0.68)</td>
</tr>
<tr>
<td>MAGE</td>
<td>1.06 (0.96-1.20) (0.23)</td>
<td>1.01 (0.91-1.11) (0.90)</td>
<td>1.16 (1.03-1.30) (0.01)</td>
<td>1.07 (0.98-1.17) (0.14)</td>
</tr>
<tr>
<td>MAGE (HbA1c)</td>
<td>1.00 (0.89-1.12) (0.95)</td>
<td>0.96 (0.86-1.06) (0.37)</td>
<td>1.09 (0.96-1.23) (0.18)</td>
<td>0.98 (0.90-10.8) (0.74)</td>
</tr>
<tr>
<td>MAGE (AUC)</td>
<td>1.00 (0.88-1.12) (0.93)</td>
<td>0.94 (0.85-1.05) (0.29)</td>
<td>1.10 (0.97-1.25) (0.13)</td>
<td>1.00 (0.91-1.10) (0.93)</td>
</tr>
<tr>
<td>SD TF</td>
<td>0.14 (0.04-0.52) (0.003)</td>
<td>0.15 (0.05-0.48) (0.001)</td>
<td>0.63 (0.13-3.07) (0.57)</td>
<td>0.16 (0.06-0.47) (0.001)</td>
</tr>
<tr>
<td>SD TF (HbA1c)</td>
<td>0.36 (0.09-1.37) (0.13)</td>
<td>0.25 (0.07-0.86) (0.03)</td>
<td>1.42 (0.26-7.71) (0.68)</td>
<td>0.62 (0.20-1.87) (0.39)</td>
</tr>
<tr>
<td>SD TF (AUC)</td>
<td>0.33 (0.08-1.39) (0.13)</td>
<td>0.26 (0.08-0.87) (0.03)</td>
<td>1.27 (0.25-6.29) (0.77)</td>
<td>0.61 (0.19-1.94) (0.40)</td>
</tr>
</tbody>
</table>

HbA1c, AUC, SD, MAGE and SD TF represent means from quarterly visit 1-16 or 1-20. Patients with a positive neuropathy score at five years/complete analysis group per parameter. All models are adjusted for baseline covariates (sex, age, disease duration, prevention cohort, randomization treatment). SD (HbA1c), MAGE (HbA1c), SD TF (HbA1c), SD (AUC), MAGE (AUC) and SD TF (AUC) are six distinct models additionally adjusted for HbA1c or AUC apart from the baseline covariates. OR, odds ratio; CI, confidence interval; AUC, area under the curve; SD, standard deviation; MAGE, mean amplitude of glycaemic excursions; SD TF, standard deviation obtained from glucose data transformed according to Kovatchev: transformed blood glucose = \(1.794^{(\log[\text{BG}]^{100c-1.861})^{14}}\).
Logistic regression analysis showed no effect of glucose variability, computed as the mean SD and mean MAGE from the seven-point glucose profiles from quarterly visit 1-20 (first 5 years), on confirmed clinical neuropathy, the main neuropathy endpoint of the DCCT (Table 2). Dividing the variability parameters in quartiles and performing the analysis per randomization group did not change the outcome (data not shown).

No effect of glycaemic variability on clinical neuropathy was seen, with exception of a small protective effect of the SD adjusted for AUC (Table 2). In addition, no effect of glycaemic variability was seen on the incidence of sensory signs (SD, 1.00 [0.82-1.22], \( P = 0.99 \); MAGE, 1.02 [0.93-1.12], \( P = 0.69 \)) as well as in separate analysis of the F-wave latency of the median nerve (SD, 1.12 [0.84-1.49], \( P = 0.44 \); MAGE, 1.03 [0.90-1.17], \( P = 0.67 \)) and the amplitude of the sural nerve (SD, 1.27 [1.00-1.60], \( P = 0.05 \); MAGE, 1.05 [0.95-1.17], \( P = 0.34 \)).

Glycaemic variability seemed to have an effect on autonomic neuropathy, but this effect disappeared when adjusting the model for HbA1c or AUC (Table 2). Analysing both randomization groups separately also did not reveal a relation over HbA1c (data not shown). Separate examination of the three autonomic function parameters showed that only for beat-to-beat heart rate variation during a Valsalva manoeuvre did the effect remain significant when adjusting for mean glucose (SD, 2.64 [1.17-5.94], \( P = 0.02 \); MAGE, 1.42 [1.07-1.90], \( P = 0.02 \)), but not when adjusting for HbA1c (SD, 1.84 [0.90-3.76], \( P = 0.09 \); MAGE 1.30 [0.98-1.72], \( P = 0.07 \)). There was no effect of glycaemic variability on beat-to-beat heart-rate variation during deep breathing and postural blood pressure testing (data not shown).

HbA1c and AUC itself were strong predictors of any form of neuropathy as described above and transformation of the individual glucose data according to Kovatchev \(^{14}\) did not alter the results (Table 2).

**Discussion**

In this study, glycaemic variability did not influence the development of neuropathy over HbA1c or mean glucose. HbA1c and mean glucose itself were strong predictors for the development of diabetic neuropathy. These results are in line with earlier analysis of DCCT data describing no influence of glycaemic variability on the development or progression of retinopathy and nephropathy \(^{7}\).

Bragd et al. \(^{6}\) found that glucose variability (SD) was a borderline predictor of the incidence of peripheral neuropathy in 100 type 1 diabetes and with a follow-up period of 11 years (\( P = 0.07 \); HR 1.73, range 0.94-3.19). Peripheral neuropathy in their study was
defined as sensory neuropathy, as indicated by monofilament testing, and an abnormal EMG and/or vibration test. This same study showed a significant relationship between SD and the prevalence of peripheral neuropathy \((P = 0.03; \text{OR} 2.34, \text{range} 1.06-5.20)\), perhaps suggesting that the nervous system may be particularly susceptible to glycaemic fluctuations. Another cross-sectional study investigated the relation between glucose variability and the presence of pain in 20 type 1 diabetes patients with established peripheral neuropathy. Compared to the group without symptoms \((n = 10)\), the group with painful symptoms had more glycaemic excursions, although there was no difference in MAGE. Since the groups were neither matched nor the effect adjusted for mean glucose, the significantly larger mean glucose in the painful group is more likely to explain the difference between the groups. In the DCCT no separate distinction was made for pain as a symptom so the outcome measure is not exactly comparable.

We did find a relation between glucose variability and two neuropathy parameters: the autonomous parameter beat-to-beat heart rate variation <20 combined with a Valsalva ratio >1.5 as well as clinical neuropathy, both independent from AUC. These results are likely the consequence of multiple testing. When adjusting for multiple testing using the Holm method a \(P\)-value of 0.0125 would be needed to reject the \(H_0\) hypothesis, which is smaller than the \(P\)-value of 0.02 and 0.04 we found for the autonomic neuropathy parameter and clinical neuropathy respectively. Multiple testing is also the most likely explanation for the odds ratio’s smaller than 1 found for some of the clinical neuropathy parameters (Table 1).

What strengthens our results is that we did not find a relationship between glucose variability and sensory signs or median motor F-wave latency and sural amplitude, the earliest indicators of diabetic neuropathy. As diabetic neuropathy is mostly a small-fibre disease, sensory signs are usually the presenting sign of the disease and they are a stable and reliable measure of disease status or progression. Although EMG studies measure large-fibre function, median motor F-wave latency and sural amplitude are the most sensitive of all EMG measures to detect diabetic neuropathy.

A limitation of this study is that the variability parameters are calculated from seven-point glucose curves by self-monitoring. Continuous glucose monitoring (CGM) might detect fluctuations occurring between two measurements that would be missed by self-monitoring of blood glucose. Also the DCCT participants did not collect all profiles as required, resulting in missing values. However, they were highly motivated, thus limiting missing data to a minimum. Another difficulty is that the neuropathy variables were infrequently scored. We decided to focus on events up to 4 (autonomic neuropathy) and 5 (clinical neuropathy) years because after 5 years of follow-up in more than 50% of the patients the glucose data has not been recorded. It might be possible that the analysis
at this point has been hampered by a power problem due to too few events. Possibly the DCCT/Epidemiology of Diabetes Interventions and Complications (EDIC) follow-up will provide more endpoints as the same neuropathy parameters assessed in the DCCT are measured in years 13 or 14 of its follow-up (2007-8; www.niddkrepository.org). These data have not yet been released.

In conclusion, glucose variability was not a risk factor separate from HbA1c or mean glucose in the development of diabetic peripheral neuropathy in the DCCT.

Acknowledgements
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