Can glycaemic variability, as calculated from blood glucose self-monitoring, predict the development of complications in type 1 diabetes over a decade?

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Abstract

Aims. – Is glycaemic variability an independent risk factor for the development of microvascular complications in addition to average glycaemia, as assessed by glycated haemoglobin (HbA1c)? In this study, an 11-year follow-up was carried out in patients with type 1 diabetes. The standard deviation of blood glucose (SDBG) concentration, an index of glycaemic variability, was calculated from self-monitored blood glucose data at baseline.

Methods. – A total of 100 patients were randomly selected from 442 consecutive type 1 diabetic patients attending our outpatients clinic. SDBG was calculated from 70 measurements taken over a period of four weeks. Onset and progression of micro- and macrovascular complications were recorded over the 11-year follow-up.

Results. – As expected, the prevalence of complications increased over time. Statistical analyses showed that HbA1c was an independent predictor of the incidence ($P = 0.004$) and prevalence ($P = 0.01$) of nephropathy. SDBG was found to be a predictor of the prevalence of peripheral neuropathy ($P = 0.03$), and showed borderline significance in predicting the incidence of peripheral neuropathy ($P = 0.07$). SDBG was also a highly significant predictor of hypoglycaemic unawareness ($P = 0.001$).

Conclusions. – We conclude that variability of blood glucose may be important in the development of peripheral neuropathy in patients with type 1 diabetes, and that the nervous system may be particularly vulnerable to glycaemic variability.

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Résumé

La variabilité glycémique, calculée à partir de l’autocontrôle, est-elle un facteur prédicatif des complications du diabète de type 1 ?

Objectifs. – La variabilité glycémique constitue-t-elle un facteur de risque indépendant de l’évolution des complications microvasculaires du diabète de type 1, à côté de la glycémie moyenne, évaluée par le taux de l’hémoglobine glyquée (HbA1c) ? La présente étude a comporté une période de suivi de 11 ans de patients atteints de diabète de type 1. L’indice de variabilité glycémique a été calculé à partir de l’intervalle de confiance des glycémies capillaires déterminées par autocontrôle à l’inclusion.

Méthodes. – Cent patients ont été sélectionnés de manière aléatoire parmi 442 diabétiques de type 1 consécutifs vus en hôpital de jour dans notre clinique. L’indice de variabilité glycémique a été déterminé à partir de 70 mesures de la glycémie capillaire réalisées par autocontrôle durant une période de quatre semaines. La survenue et l’évolution des complications microvasculaires ont été enregistrées à l’inclusion et durant les 11 années de suivi.

Résultats. – Comme attendu, la fréquence des complications a augmenté au fil du temps. L’analyse statistique a montré que l’HbA1c était un facteur prédicatif indépendant de l’incidence ($P = 0.004$) et de la prévalence ($P = 0.01$) de la néphropathie. L’indice de variabilité glycémique était un facteur prédicatif de la prévalence de la neuropathie périphérique ($P = 0.03$), avec une tendance comme facteur prédicatif de la survenue de celle-ci ($P = 0.07$). L’indice de variabilité glycémique était, enfin, un facteur prédicatif de survenue de non-perception de l’hypoglycémie ($P = 0.001$).

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Conclusions. – Ces données suggèrent que la variabilité glycémique pourrait jouer, chez les diabétiques de type 1, à côté de la glycémie moyenne, un rôle important dans la survenue et l’évolution de la neuropathie périphérique et que le tissu nerveux pourrait être particulièrement vulnérable à la variabilité glycémique.

Keywords: Diabetes; Type 1 diabetes; Complications; Hypoglycaemia unawareness; Microangiopathy; Neuropathy; Nephropathy; Risk factors; Glycaemic variability; Longitudinal study

Mots clés : Diabète de type 1 ; Variabilité glycémique ; HbA\textsubscript{1c} ; Non-perception des hypoglycémies ; Microangiopathie ; Neuropathie ; Néphropathie ; Facteurs de risque ; Étude longitudinale

1. Abbreviations

- SDBG: standard deviation of blood glucose
- DCCT: diabetes control and complications trial
- MI: myocardial infarction
- CVA: cerebrovascular accident
- S.D.: standard deviation
- BMI: body mass index
- CSII: continuous subcutaneous insulin infusion

2. Introduction

Chronic glycemic exposure, including the degree and duration of plasma hyperglycaemia, is thought to be the most important modifiable risk factor for complications of diabetes [1–3]. In a multivariate analysis, HbA\textsubscript{1c} level, duration of diabetes and – to a lesser degree – age at the onset of diabetes appear to be the main significant risk factors for diabetic complications [4]. In the diabetes control and complications trial (DCCT), development of microvascular complications was strongly related to HbA\textsubscript{1c} levels [5]. As a sign of glycemic memory, the reduced risk of progressive retinopathy and nephropathy, as a result of intensive therapy in these patients, persisted for at least a further 4 years despite increasing hyperglycaemia, as demonstrated in the post-study follow-up [6].

In addition, subgroup analyses of the DCCT cohort demonstrated that 8% of intensively treated subjects, compared with 20% of non-intensively treated patients with similarly elevated HbA\textsubscript{1c} levels, developed retinopathy within 9 years, a finding which has been quoted to support the notion that there is “something unique” with intensive treatment independent of HbA\textsubscript{1c} levels [7]. The question then arises as to why there is such a difference, and it may be speculated that it is due to reduced glycemic variability in intensively treated patients. Clinical studies have documented that long-term variability of fasting glucose is an independent predictor of mortality in patients with type 2 diabetes [8], and data based on the DCCT cohort suggest that, while updated mean blood glucose was the primary risk factor for mortality, the mean amplitude of glycemic excursions (MAGE) recorded at baseline in one multivariate analysis also contributed significantly to mortality [9].

Further support for the idea that glucose variability affects the risk of microvascular complications comes from another study in which the incidence of retinopathy in adolescents with type 1 diabetes appeared to fall substantially between 1990 and 2002, despite little change in HbA\textsubscript{1c} levels during that time period. In that study, the authors concluded that switching to multiple-injection regimens over time may have contributed to the improvement by reducing glycaemic fluctuations despite stability in the mean glucose concentration [10].

However, Kilpatrick et al. [11], who published the 2006 results from a statistical analysis of the large DCCT database, reported that HbA\textsubscript{1c} – but not glucose variability – was associated with a long-term risk of developing microangiopathy. The authors concluded that pre- and postprandial glucose values were equally predictive of small-vessel complications in type 1 diabetes. Neuropathy was, however, not analyzed in their report, and it is not known whether the nervous system is particularly vulnerable to glucose variability.

Specific tools have been developed to evaluate same-day glycemic variations (MAGE), day-to-day glycemic variations or excursions (mean of daily differences [MODD]), meal-related glycemic excursions (mean indices of meal excursions [MIME]) and the risk of severe hypoglycaemia expressed as the low blood glucose index (LBGI) [12]. These methods are, however, relatively laborious. In contrast, the SDBG is an easily available glucose index that has been extensively used to identify significant glycemic characteristics in clinical trials over the past decade; also, virtually all of the current glycemic-control software packages include calculation of S.D. Furthermore, in a previous study, we have shown that SDBG measurements are highly reproducible ($r=0.90, P<0.0001$) when assessed over a period of 12 months [13]. Studies have also established that this measure of glucose control is not related to HbA\textsubscript{1c} [14].

On the basis of SDBG data generated through self-monitoring of blood glucose, we hypothesized that blood glucose variability can predict the development of diabetic complications in patients with type 1 diabetes over a decade.

3. Patients and methods

In 1990, from 442 consecutive type 1 diabetic patients who attended the diabetes outpatients clinic at Danderyd Hospital, 142 were randomly selected by date of birth to participate in a study to measure blood glucose variability, as determined by frequent capillary blood glucose values obtained through stratified home-based monitoring. Of these, 100 patients agreed to participate and, thus, became the cohort in which SDBG was calculated, based on 70 measurements taken over a period of 4 weeks. The capillary tests were performed before break-
fast, before lunch, before dinner, 1.5 h after dinner and before going to bed on every other day for 4 weeks. The results of this investigation were reported elsewhere in 1994 [15]. These same patients comprised the present study cohort, which has now been re-analyzed after 11 years in terms of established risk factors for the onset and progression of micro- and macroangiopathy as well as peripheral neuropathy. During the follow-up period, the patients visited our outpatient clinic two to four times a year, according to the established clinical study protocol.

Diabetic complications were defined and categorized in 1990 as follows. Nephropathy was defined as either microalbuminuria (MA) (albumin excretion 30–300 mg/24 h) or albuminuria (albumin excretion greater than 300 mg/24 h). Retinopathy was defined as proliferative diabetic retinopathy, as determined by an expert in our research team using a blinded procedure. Peripheral neuropathy was defined as sensory neuropathy, as indicated by pathological thresholds revealed by neurometry and/or a vibration test with tuning fork and monofilament testing. Autonomic neuropathy was defined as the clinical diagnosis of erectile dysfunction, bladder dysfunction, orthostatic hypotension and/or gastroparesis. Unawareness of hypoglycaemia was defined as a documented plasma glucose value less than 3.0 mmol/L with no observable symptoms of hypoglycaemia [16]. Macroangiopathy was defined as a blood pressure greater than 140/85 mmHg and/or ongoing antihypertensive therapy, a clinical diagnosis of angina pectoris, intermittent claudication, MI and/or CVA.

Clinical data, including medical history, diabetic complications, blood pressure, laboratory tests and pharmaceutical therapy, were extracted from each patient’s medical records. HbA1c was measured by liquid chromatography assay (reference value for healthy subjects less than 5.2%). SDBG values obtained at baseline were used in the statistical evaluations.

Crude comparisons for quantitative variables were made by t test, and associations between categorical variables were made by Chi-square tests. The prevalence of complications—those present at the start of the follow-up period—was analyzed using multivariable logistic-regression models, including gender and age, duration of diabetes, mean HbA1c of the yearly recorded values prior to the start of follow-up and SDBG as continuous variables. The results of these analyses are presented as odds ratios (OR) per unit of measurement with 95% confidence intervals (CI). The rate of complications during the follow-up was crudely estimated as the number of events divided by person-years at risk. Person-years at risk were calculated as the time interval from the start of follow-up to either the end of follow-up, death, being lost to follow-up or the considered complication—whichever came first. Multivariable analyses of factors influencing the incidence of complications were performed using Cox regression models with discrete time scales. The models included the same covariables as the logistic-regression model and the mean HbA1c was, in these models, introduced as a time-dependent variable. Results of these analyses are presented as hazard ratios (HR) per unit of measurement with a 95% CI.

4. Results

The analyses were based on data taken from the cohort in 1990 (N = 100), 1995 (N = 95) and 2001 (N = 81) (Table 1). There was a slight preponderance of men (56%) in 1990. The mean age of the patients in 1990 was 45 years, with a range of 19–78 years, and their mean duration of diabetes was 20 years, with a range of 2–62 years. In the 1990 cohort, insulin pumps were used by 8%, and only 4% of patients were not using multiple injections or pumps; 9% were considered to have unawareness of hypoglycaemia. Glycaemic control was relatively poor, with a mean HbA1c of 8.1%. Of the 100 patients, the use of CSII increased by 27%, and their BMI increased slightly over time.

In the follow-up analysis, we found that 17 patients had died. These patients were older, and had longer disease durations and more complications at inclusion, but did not differ in SDBG. Death certificates listed the cause of death as MI in five patients, CVA in four patients, heart failure in four patients, hypoglycaemia in three patients and Huntington’s chorea in one patient. A further two patients had emigrated from Sweden and were lost to follow-up.

At baseline, no patient presented with findings indicative of proliferative retinopathy and only 9% had nephropathy, while 29% had evidence of peripheral neuropathy. As expected, micro- and macrovascular complications became more prevalent during the follow-up period, and the most prominent complication was peripheral neuropathy (Table 2).

Table 3 presents the mean SDBG and HbA1c measures for patients with and without complications at baseline, as well as for those who developed complications during follow-up. Interestingly, SDBG was significantly higher in the patients with complications compared with those without, although HbA1c did not differ significantly except in cases of nephropathy.

Multivariate analyses of the data, adjusted for HbA1c, age and disease duration, revealed that HbA1c was an independent predictor of the prevalence (P = 0.01; OR 2.77, range 1.23–6.27) and incidence (P = 0.004; HR 2.64, range 1.37–5.11) of nephropathy, but did not correlate to the prevalence of peripheral neuropathy (P = 0.26; OR 1.45, range 0.76–2.76). However, it had borderline significance in relation to the incidence of peripheral neuropathy (P = 0.06; HR 1.53, range 0.99–2.37), but no relationship to the incidence of retinopathy (P = 0.6; HR 1.18, range 0.60–2.33).

Table 1

<table>
<thead>
<tr>
<th>Clinical data from 1990, 1995 and 2001</th>
<th>1990 (N = 100)</th>
<th>1995 (N = 95)</th>
<th>2001 (N = 81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men (%)</td>
<td>56</td>
<td>56</td>
<td>55</td>
</tr>
<tr>
<td>Age (years)</td>
<td>44.7 ± 13.2</td>
<td>49.3 ± 13.1</td>
<td>54.6 ± 12.5</td>
</tr>
<tr>
<td>Duration of type 1 diabetes (years)</td>
<td>19.7 ± 11.0</td>
<td>24.5 ± 10.8</td>
<td>28.6 ± 10.4</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.1 ± 1.2</td>
<td>7.5 ± 1.5</td>
<td>7.2 ± 0.9</td>
</tr>
<tr>
<td>Body mass index</td>
<td>23.2 ± 2.4</td>
<td>24.2 ± 2.9</td>
<td>25.2 ± 3.9</td>
</tr>
<tr>
<td>Insulin dose (U/24 h)</td>
<td>40.8 ± 12.3</td>
<td>40.7 ± 12.2</td>
<td>42.0 ± 12.5</td>
</tr>
<tr>
<td>CSII (%)</td>
<td>8</td>
<td>24</td>
<td>35</td>
</tr>
</tbody>
</table>

Data are expressed as means ± S.D.
CSII: continuous subcutaneous insulin infusion.
Table 2  
Prevalence and incidence data of diabetic complications

<table>
<thead>
<tr>
<th></th>
<th>Prevalence 1990 (%)</th>
<th>Incidence 1990–2001 (n)</th>
<th>Incidence (rate/100 patient-years)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Macroangiopathy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension, or medication with antihypertensive drugs</td>
<td>15</td>
<td>18</td>
<td>3.0</td>
</tr>
<tr>
<td>Myocardial infarction/angina</td>
<td>6</td>
<td>9</td>
<td>1.2</td>
</tr>
<tr>
<td>Claudication</td>
<td>8</td>
<td>8</td>
<td>1.1</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>1</td>
<td>8</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Nephropathy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>11</td>
<td>1.4</td>
</tr>
<tr>
<td><strong>Neuropathy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral</td>
<td>29</td>
<td>21</td>
<td>3.7</td>
</tr>
<tr>
<td>Autonomic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>orthostatic hypotension</td>
<td>1</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>erectile dysfunction</td>
<td>4</td>
<td>13</td>
<td>3.0</td>
</tr>
<tr>
<td>gastrointestinal dysfunction</td>
<td>5</td>
<td>16</td>
<td>1.9</td>
</tr>
<tr>
<td><strong>Retinopathy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proliferative diabetic retinopathy</td>
<td>0</td>
<td>10</td>
<td>1.2</td>
</tr>
<tr>
<td><strong>Hypoglycaemic unawareness</strong></td>
<td>9</td>
<td>15</td>
<td>2.0</td>
</tr>
</tbody>
</table>

However, SDBG was significantly related to the presence of peripheral neuropathy ($P=0.03$; OR 2.34, range 1.06–5.20) and was also of borderline significance as a predictor of its incidence ($P=0.07$; HR 1.73, range 0.94–3.19). However, statistical analyses did not reveal any significant relationships between SDBG and the incidence of proliferative retinopathy ($P=0.28$; HR 1.37, range 0.77–2.43), or of nephropathy ($P=0.10$; HR 1.75, range 0.89–3.40) or its prevalence ($P=0.35$; OR 1.39, range 0.70–2.76). In fact, we found SDBG to be an independent predictor of the prevalence of peripheral neuropathy, with no confounding effects due to age, diabetes duration or HbA1c levels. SDBG was also a highly significant predictor of the incidence of hypoglycaemic unawareness ($P=0.001$; HR 2.66, range 1.48–4.80).

5. Discussion

In the analysis of our cohort of type 1 diabetic patients followed for 11 years, we found SDBG to be an independent predictor of the prevalence of peripheral neuropathy as well as a predictor, with borderline significance, of its incidence. SDBG was also a strong predictor of hypoglycaemic unawareness. However, we could find no significant relationship between SDBG and retinopathy or nephropathy. As we had defined retinopathy very narrowly (as proliferative retinopathy), and its incidence as well as that of nephropathy appeared to be low in our cohort compared with other clinic-based studies, it may be that our study had insufficient power to detect such relationships – if any were present.

Kilpatrick et al. [11] could also find no correlation between glucose variability and the relative risk of developing microangiopathic (nephropathy and retinopathy) complications. They used 7-point blood-glucose profiles, taken at 3-month intervals, which yielded an aggregate of 24,652 capillary blood glucose profiles between the prebreakfast (07h00) and bedtime (22h00) periods. Instability of blood glucose (same-day S.D.), calculated as the S.D. of daily blood glucose variability over time, was estimated to be the S.D. of the mean blood glucose measurements taken at each quarter. They found that glucose variability played no role in the development of microvascular complications and concluded that only elevation of mean glucose over time, as expressed by HbA1c, was associated with a proportionally greater risk of developing microangiopathy over the long term.

Peripheral neuropathy, however, was not analyzed in their report, and the question of the relationship between glycaemic variability and peripheral neuropathy, in our opinion, remains open. In one previous clinical study, a relationship between

Table 3  
Mean SDBG and mean HbA1c in 1990 patients with and without complications at baseline, and in those who developed complications, during study period 1990–2001

<table>
<thead>
<tr>
<th></th>
<th>Free of complications at baseline</th>
<th>With complications at baseline</th>
<th>Incidence of complications 1990–2001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unawareness SDBG</td>
<td>3.8 ± 1.0</td>
<td>4.3 ± 1.3</td>
<td>4.5 ± 0.8</td>
</tr>
<tr>
<td>HbA1c</td>
<td>7.9 ± 1.4</td>
<td>7.4 ± 0.6</td>
<td>7.6 ± 1.1</td>
</tr>
<tr>
<td>Nephropathy SDBG</td>
<td>3.8 ± 0.8</td>
<td>4.6 ± 1.2</td>
<td>4.4 ± 1.6</td>
</tr>
<tr>
<td>HbA1c</td>
<td>7.6 ± 1.2</td>
<td>8.4 ± 1.1</td>
<td>8.5 ± 1.4</td>
</tr>
<tr>
<td>Retinopathy SDBG</td>
<td>3.9 ± 1.0</td>
<td>–</td>
<td>4.2 ± 1.3</td>
</tr>
<tr>
<td>HbA1c</td>
<td>7.8 ± 1.3</td>
<td>–</td>
<td>8.0 ± 1.2</td>
</tr>
<tr>
<td>Neuropathy SDBG</td>
<td>3.7 ± 0.9</td>
<td>4.4 ± 1.1</td>
<td>4.0 ± 0.8</td>
</tr>
<tr>
<td>HbA1c</td>
<td>7.5 ± 1.3</td>
<td>7.9 ± 1.0</td>
<td>8.2 ± 1.4</td>
</tr>
</tbody>
</table>

* Within-group statistical significance.
blood glucose excursions and painful neuropathy was clearly documented [17]. At a given level of HbA1c, high variability in measured glucose can increase the number of both hyper- and hypoglycaemic excursions. The latter, if recurrent, can induce a state of hypoglycaemic unawareness which, in itself, is a major risk factor for severe hypoglycaemic events in patients with type 1 diabetes [16–19].

In the present study, we were able to verify that SDBG was a highly significant predictor of the incidence of hypoglycaemic unawareness. This raises the question of a putative relationship between hypoglycaemia and peripheral neuropathy. In animal experiments, hypoglycaemia can cause distal axonopathy, including both degenerative and regenerative events; in this case, motor neuron axons appear to be more vulnerable than sensory axons [20]. In a previous review of the literature, we could find no studies showing that the development of peripheral neuropathy in diabetic patients could unequivocally be attributed to hypoglycaemia [21].

The mechanisms involved in the development of diabetic complications such as peripheral neuropathy are usually described as beginning with sustained periods with hyperglycaemia, which leads to intracellular overproduction of superoxide. The formation of superoxide is regarded as the key event in the activation of all other pathways, such as the polyol/sorbitol pathway flux, increased advanced glycation end-product formation, increased hexosamine flux and activation of oxidative stress. The effect of variable blood glucose – with periods of high glucose levels followed by periods of low levels, or vice versa – could, in this case, be more deleterious to neural fibres than to other tissues. A nerve fibre might, for example, be triggered by an episode of hypoglycaemia and then, following that, become more vulnerable to high glucose levels. The damage might become sustained through one of the ordinary mechanisms – for example, the polyol/sorbitol pathway – believed to be involved in the development of complications.

One limitation of our study is the small number of patients in our cohort. Nevertheless, given our long, 11-year, follow-up, we believe that our findings are valid in suggesting a role of glycaemic variability in the pathogenesis of peripheral neuropathy. Another limitation of our study is that we did not assay a range of factors that, from a theoretical point of view, could have mediated the glycaemic effects on vascular complications including, for example, haemorrhheological abnormalities (platelet activation, fibrinogen levels) and endothelial cell dysfunction (von Willebrand factor, cell adhesion molecules). Another possible limiting factor is the question of reverse causality, which cannot be ascertained in an observational study such as the present investigation. For clarification of such an issue, a randomized clinical trial is mandatory.

We conclude that variability of blood glucose may be important in the development of peripheral neuropathy in patients with type 1 diabetes, and put forward the hypothesis that the nervous system may be particularly vulnerable to glycaemic variability. We also welcome further studies of this issue – in particular, those including continuous glucose monitoring to assess MAGE – to elucidate our hypothesis.

References