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ScienceDirect
Diabetes & Metabolism 34 (2008) 612–616
Diabetes & Metabolism
http://france.elsevier.com/direct/diabet

Original article

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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Received 21 December 2007; received in revised form 16 April 2008; accepted 25 April 2008
Available online 27 September 2008

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 (HbA_{1c})? 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 HbA_{1c} 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.

Résumé

La variabilité glycémique, calculée à partir de l'autocontrôle, est-elle un facteur prédictif 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 (HbA_{1c}) ? 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'HbA_{1c} était un facteur prédictif 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 prédictif de la prévalence de la neuropathie périphérique ($P = 0{,}03$), avec une tendance comme facteur prédictif de la survenue de celle-ci ($P = 0{,}07$). L'indice de variabilité glycémique était, enfin, un facteur prédictif de survenue de non-perception de l'hypoglycémie ($P = 0{,}001$).

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doi:10.1016/j.diabet.2008.04.005

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_{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 glycaemic 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_{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_{1c} levels [5]. As a sign of glycaemic 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_{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_{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 glycaemic 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 glycaemic 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_{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_{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 glycaemic variations (MAGE), day-to-day glycaemic variations or excursions (mean of daily differences [MODD]), meal-related glycaemic 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 glycaemic characteristics in clinical trials over the past decade; also, virtually all of the current glycaemic-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_{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-