High day-to-day glucose variability: A frequent phenomenon in children and adolescents with type 1 diabetes attending summer camp

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Abstract

Background. – Day-to-day glucose variability may cause difficulty for patients trying to adjust their insulin dosages and for healthcare providers when they have to make recommendations. The aim of this research was to evaluate the frequency of high variability in a population of diabetic children and adolescents attending summer camp.

Methods and Results. – The mean of the daily differences (MODD) in glucose concentrations was calculated from continuous glucose monitoring (CGM) over five consecutive days in 6 diabetic patients. This index was correlated to the MODD calculated from pre-meal and bedtime blood glucose (BG) measurements ($r=0.87$). We used the MODD calculated on these four BG measurements for five consecutive days to evaluate day-to-day glucose variability in 100 young diabetic patients treated with glargine and ultrarapid analogue insulin. Only one child had a MODD value lower than 36 mg/dl, considered a threshold for high day-to-day variability, and 94 children had a MODD value higher than 45 mg/dl. The median value was 78 mg/dl. The expected positive correlation between the MODD and its standard deviation ($r=0.32$, $P<0.01$) suggested that the greater the day-to-day variability, the more variable the variability across five consecutive days.

Conclusions. – The estimation of MODD from four pre-meal BG values correlated to that from CGM, and may represent a simple index of day-to-day glycaemic variability. High day-to-day glucose variability in glucose profile is frequently observed in diabetic children attending summer camp.

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Résumé

Variabilité inter-quotidienne importante de la glycémie dans le diabète de type 1 : un problème fréquent chez les enfants et adolescents présentant un diabète de type 1, participant à un camp de vacances.

Objectif. – La variabilité glycémique inter-quotidienne peut représenter une difficulté pour les patients qui veulent adapter leurs doses d’insuline et pour les médecins qui doivent proposer des recommandations. Le but de ce travail a été d’évaluer la fréquence de cette variabilité élevée dans une population d’enfants et d’adolescents diabétiques participant à un camp de vacances.

Méthodes et résultats. – L’indice Mean of daily differences (MODD) a été calculé à partir de cinq jours consécutifs d’enregistrement de CGM chez six patients diabétiques. Cet indice était corrélé au MODD calculé sur les trois glycémies préprandiales et la glycémie au coucher ($r=0.87$). Nous avons utilisé ce MODD calculé à partir de quatre glycémies quotidiennes sur cinq jours consécutifs pour évaluer la variabilité glycémique inter-quotidienne chez 100 jeunes patients diabétiques traités par glargine et insuline analogue ultrarapide. Un seul enfant avait un MODD inférieur à 36 mg/dl, ce qui est le seuil au delà duquel on considère que la variabilité glycémique inter-quotidienne est élevée, et 94 enfants avaient un MODD supérieur à 45 mg/dl. La valeur médiane était de 78 mg/dl. La corrélation positive entre la valeur moyenne du MODD et sa déviation standard ($r=0.32$, $P<0.01$), bien qu’attendue, suggère que plus la variabilité inter-quotidienne est importante, plus elle est elle-même variable sur une période de cinq jours.

Conclusion. – L’indice MODD estimé à partir de quatre glycémies quotidiennes, étant corrélé à celui déterminé à partir de CGM, peut représenter un outil simple de mesure de la variabilité glycémique inter-quotidienne. Il est fréquent d’observer une variabilité élevée dans les profils glycémiques chez les enfants et adolescents participant à un camp de vacances.

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Keywords: Day-to-day variability; MODD; CGM; Insulin adjustment

Mots clés : Variabilité glycémique inter-quotidienne ; MODD ; CGM ; Adaptation des doses d’insuline

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1. Introduction

In daily life, diabetic patients are confronted with glycaemic fluctuations, and it is important to distinguish variations during a given day from variations from one day to the next. The first kind of fluctuation can be estimated using different indices, such as the standard deviation (SD) of recorded blood glucose values or the mean amplitude of glycaemic excursions (MAGE) index [1]. The second kind of fluctuation indicates that the glycaemic pattern may vary on two consecutive days. This day-to-day variability can be estimated as the difference between blood glucose values determined at the same time on two consecutive days (the mean of daily difference or MODD) [2].

This day-to-day variability has several causes [3]: variability in carbohydrate intake, in exercise, but also in the resorption of insulin from injection sites [4,5] because of marked lipohypertrophy [6,7] or inadequate resuspension of nonsoluble insulin preparations [8]. Whatever the mechanism, day-to-day variability may have harmful consequences. It may exacerbate the fear of hypoglycaemia [9], and may render patients reluctant to intensify insulin therapy [10]. On the other hand, inconsistency in blood glucose patterns may jeopardize the rationale leading to decisions concerning insulin dose adjustments by the patient, but also by the healthcare provider (HCP). In a recent study, within- and between-day blood glucose variability was found to correlate to HbA1c in patients on multiple daily injections [11].

The aim of this research was to provide a simple method for assessing day-to-day variability, using only three pre-meal and one bedtime values. We found that the day-to-day variability index, computed from only these four blood glucose measurements, was significantly correlated in six patients to an index calculated from five consecutive daily recordings with continuous glucose monitoring using a subcutaneous sensor. Based on this finding, we determined this four-measurement day-to-day variability index in 100 children with type 1 diabetes, treated with a basal–bolus insulin regimen using glargine and ultrarapid analogue insulin, who were attending a diabetes summer camp.

2. Subjects, materials and methods

2.1. Continuous glucose monitoring system

For this study, we used continuous glucose recordings obtained in six type 1 diabetic patients. This monitoring system, using a wire glucose sensor and an electronic control unit, has been described elsewhere [12]. Five daily recordings were obtained for all patients. Fig. 1 is an example of a continuous glucose estimation compared with frequent capillary blood glucose measurements using an Accu-chek Active Glucometer (Roche Diagnostics). In this study, the sensor was calibrated three times a day using a one-point calibration procedure [13].

2.2. Estimation of day-to-day variability

For each of the six five-day recordings, the MODD index — referred to as the CGM–MODD — was calculated as the absolute mean of daily blood glucose differences of paired blood glucose values on successive days [2], and this was done for each of the four day-to-day intervals. From the same recordings, we also calculated a MODD value — referred to as BG–MODD — using only the four blood glucose measurements determined before each meal and at bedtime.

![Continuous glucose estimation](image)

Fig. 1. Continuous glucose estimation measured by a subcutaneous glucose sensor (continuous line) compared with frequent capillary blood glucose concentration (closed circle) in a type 1 diabetic patient (#1) over five days. Glucose estimation was obtained with a one-point calibration performed three times per day (before each meal).
2.3. Assessment of BG–MODD in type 1 diabetic patients

We obtained the logbook pages from 100 type 1 diabetic children and teenagers who attended summer camp with Aide aux jeunes diabétiques (14.7 ± 1.3 years, HbA1c: 8.5 ± 1.6%). The BG–MODD was calculated as described above using the data from five consecutive days. In each patient, we calculated the means and SD of the four BG–MODD values observed during these five days.

3. Results

3.1. CGM-assessed between-day glucose variability

Fig. 2 shows the blood glucose profiles obtained on five consecutive days in a diabetic patient. At first glance, the glucose pattern appears to be reproducible. However, the MODD values indicated that it was both high and variable, ranging from 59 to 144 mg/dl. Fig. 3 presents the CGM–MODD values obtained in

Fig. 3. Evolution of CGM–MODD values calculated from five days of continuous glucose monitoring using a subcutaneous glucose sensor in six type 1 diabetic patients. Each CGM–MODD value was calculated for two consecutive days.
the six patients. Only three of the 24 values were below 36 mg/dl and four of the 24 were below 45 mg/dl.

Fig. 4 shows the three pre-meal and one bedtime capillary blood glucose levels for the same patient as in Fig. 2. Here, too, the BG–MODD estimation ranged from 34 to 165 mg/dl, and was positively correlated to the CGM–MODD values determined for this patient ($y = 1.60x – 68.0, r = 0.96$). Table 1 shows the correlation equations obtained for all six patients.

### 3.2. BG–MODD estimation in 100 diabetic patients

Fig. 5 presents the BG–MODD estimations observed in 100 diabetic children and adolescents treated with a basal–bolus insulin regimen. The data shown are the means and SD of the four day-to-day values recorded for each patient. The mean value was higher than 36 mg/dl in 99 patients and higher than 45 mg/dl in 94. The median value was 78 mg/dl. There was a positive correlation between the BG–MODD value and its SD ($r = 0.32, P < 0.01$).

### Table 1

<table>
<thead>
<tr>
<th>Patients</th>
<th>$y = ax + b$</th>
<th>$r$</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>1.6x + 68.0</td>
<td>0.96</td>
</tr>
<tr>
<td>#2</td>
<td>1.0x + 7.6</td>
<td>0.79</td>
</tr>
<tr>
<td>#3</td>
<td>1.3x – 45.8</td>
<td>0.87</td>
</tr>
<tr>
<td>#4</td>
<td>0.6x + 7.1</td>
<td>0.73</td>
</tr>
<tr>
<td>#5</td>
<td>0.8x + 6.7</td>
<td>0.98</td>
</tr>
<tr>
<td>#6</td>
<td>0.5x – 3.1</td>
<td>0.87</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>(1.0 ± 0.4)x + (6.8 ± 36.4)</td>
<td>0.87 ± 0.10</td>
</tr>
</tbody>
</table>

### 4. Discussion

In this study, we first demonstrated in six patients that the estimation of day-to-day glucose variability (MODD) based on pre-meal and bedtime blood glucose values is reasonably well correlated to the MODD estimated from continuous glucose monitoring. Using this four-measurement BG–MODD index, we observed important day-to-day glycaemic variability in 100 young diabetic patients, treated with a basal–bolus insulin regimen using multiple daily injections of glargine at bedtime, and aspart or lispro before meals, who were attending a diabetes summer camp. The median value of this BG–MODD index was approximately 80 mg/dl, and was almost always higher than 36 mg/dl, the threshold considered by Molnar as defining high day-to-day variability [2].

Such a high day-to-day variability may have important consequences on the daily lives of patients. First, it may contribute to the fear of hypoglycaemia [9], exacerbated by the unexpected way in which it may happen, at any time. Interestingly, we observed a positive correlation between BG–MODD value and its SD ($r = 0.32, P < 0.01$). This was statistically to be expected. However, from a practical point of view, the fact that, the greater the day-to-day variability, the more variable was the variability across five consecutive days may serve to reinforce the feeling of insecurity in these patients. Indeed, fear of hypoglycaemia was found to be, in all age groups, an impediment to the clinical implementation of the results of the Diabetes Control and Complications Trial (DCCT) [10].

Also, this variability may make it difficult for patients to adjust their insulin dosages, as the use of retrospective algorithms (increase your morning insulin doses, if on three
In the same way, glycaemic day-to-day variability may make it difficult for the healthcare provider to propose any changes in insulin therapy to improve glycaemic control. This problem can occur either in discontinuous conventional monitoring recorded in a logbook or when the HCP has to decide on insulin adjustments based on continuous glucose monitoring [15–27]. A recent study in diabetic pregnant women [28] suggested that, if the day-to-day glucose daily difference is higher than 45 mg/dl, decisions taken on two separate day profiles will frequently be inconsistent. In the present study, we observed that nine out of 10 diabetic children or adolescents have a day-to-day variability much greater than this threshold when placed in a situation of variable activities and mealtimes, such as a summer camp for diabetic children, in spite of the close surveillance of healthcare providers to maintain metabolic control of the children every day. Alemzadeh found mean CGM-assessed MODD values of $41 \pm 35$ mg/dl and $44 \pm 30$ mg/dl in diabetic adolescents using CSII and MDI, respectively [6], the large SD value suggesting that high between-day glucose variability may not be restricted to the summer camp situation of our study. In his study, Pickup evaluated the day-to-day variability in diabetic adults using multiple daily injections as the SD of the pre-breakfast blood glucose concentration on consecutive days, and found a mean value of $75 \pm 21$ mg/dl [11].

In conclusion, this report offers a simple method, based on only four blood glucose measurements that patients are generally accustomed to perform, for estimating the day-to-day variability of their glycaemic pattern. It may also be useful for evaluating the reproducibility of new insulin analogues. In addition, these data introduce a note of caution into the interpretation of a CGM recording, especially if only two or three days’ measurements are covered. Our findings indicate that day-to-day variability must be taken into account in the interpretation of CGM recording. It may explain in part the scarcity of studies demonstrating a positive effect of its use on HbA1c: among all randomized studies evaluating the role of continuous glucose monitoring [19–27], only two demonstrated a significant decrease in HbA1c [24,25].

References


