Mini-Review

Continuous glucose monitoring in patients with type 2 diabetes: Why? When? Whom?

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Abstract

The overall assessment of glycaemic control in patients with type 2 diabetes should normally include the monitoring of three parameters that are usually depicted as the ‘glucose triad’: HbA1c, fasting plasma glucose (FPG) and postprandial glucose (PPG) excursions. However one additional marker, the so-called ‘glucose variability’ might be as important as the three others since it has been demonstrated that both upward and downward glucose fluctuations are potent activators of oxidative stress. Even though many methods have been proposed for assessing glucose fluctuations, the ‘mean amplitude glucose excursions’ (MAGE) index remains the ‘gold standard’. However MAGE estimation requires the use of continuous glucose sensors. Despite the debate on the reliability and cost of the devices that permit glucose monitoring, we suggest that interventional trials designed to evaluate the effects of glucose fluctuations on diabetic complications should benefit from the use of continuous glucose monitoring systems (CGMSs). More prosaically, the use of these technologies could be extended to current clinical care of type 2 diabetic patients especially for motivating them to accept earlier insulin treatments in case of ‘oral antidiabetic drug secondary failure’, and further for choosing the most appropriate insulin regimen.

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Résumé

Enregistrement glycémique continu dans le diabète de type 2 : pourquoi, quand et comment ?

L’estimation globale de l’équilibre glycémique dans le diabète de type 2 devrait normalement inclure la surveillance de 3 paramètres qui sont habituellement décrits en tant que composants de la « triade glucose » : l’HbA1c, la glycémie à jeun et les excursions glycémiques postprandiales. Toutefois, un marqueur supplémentaire, destiné sous le terme de « variabilité glycémique » pourrait être aussi important que les 3 autres puisqu’il a été démontré que les fluctuations ascendantes et descendantes de la glycémie sont de puissants activateurs potentiels du stress oxydatif. Bien que plusieurs méthodes aient été proposées pour évaluer les fluctuations glycémiques c’est l’index MAGE « mean amplitude glucose excursions » qui reste la méthode de référence. Toutefois l’estimation du MAGE nécessite l’utilisation d’un enregistrement continu de la glycémie. En dépit des discussions sur la fiabilité et le coût des dispositifs qui permettent l’enregistrement glycémique, nous suggérons que les essais interventionnels destinés à évaluer les effets des fluctuations glycémiques sur les complications diabétiques devraient bénéficier de l’utilisation des systèmes d’enregistrement continu de la glycémie. De manière plus banale, l’emploi de ces technologies pourrait être étendu à l’exploration clinique de routine des diabétiques de type 2 en particulier pour les motiver à accepter des traitements insuliniques plus précoces en cas d’échec secondaire des antidiabétiques oraux et au-delà, pour choisir le schéma insulinique le plus adéquat.

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1. Introduction

Glycaemic control in patients with type 2 diabetes is usually assessed by the measurements of the three following markers: HbA1c, fasting plasma glucose (FPG) and postprandial glucose (PPG). These markers considered as a whole are commonly depicted as the ‘glucose triad’ [1]. At present, there is no doubt that a satisfactory monitoring of the ‘dysglycaemia’ that characterizes type 2 diabetes implies an HbA1c testing every 3–4 months [2,3]. However the debate is largely open concerning the timing and the frequency at which both FPG and PPG should be checked [4–6]. Our position is that regular testing by using self monitoring of blood glucose (SMBG) is highly recommended in patients with type 2 diabetes [7] even in those patients who are only treated with oral antidiabetic drugs (OAD). This opinion is based on several observations. Firstly the contribution of PPG excursions to overall hyperglycaemia is never negligible, secondly this contribution becomes predominant in all type 2 diabetic patients who exhibit HbA1c levels below 7–7.5% [8,9]. However recent data suggest that the evaluation of the glucose triad is not sufficiently informative for providing a full picture of the diabetic ‘dysglycaemia’ [10–12]. The purpose of the present review is to address this issue and to discuss why and when the use of new technologies such as the so-called continuous glucose monitoring system (CGMS) [13] can be helpful for future interventional trials or even at present for the current clinical care of patients suffering from type 2 diabetes.

2. Continuous glucose monitoring in clinical trials: Why?

In a recent study [12], we have demonstrated that glucose fluctuations calculated from the mean amplitude glucose excursions (MAGE) as described by Service et al. [14,15] are potent activators of oxidative stress in type 2 diabetic patients even when they are solely treated with OAD. Such observations raise the question to know whether we have first to enlarge the concept of the ‘glucose triad’ to such parameters as acute glucose fluctuations and to further minimize the glycaemic variability in order to prevent diabetic complications [10,11]. These two questions are actually under cross fire and an appropriate answer needs several problems and controversies to be solved in the near future.

2.1. Do we have appropriate tools for assessing glucose variability?

Several approaches have been used to quantify the amplitude of glycaemic fluctuations: standard deviation (S.D.) of glucose levels [16], differences between minimum and maximum glucose levels, mean peak-to-nadir differences of glucose levels, percentage of glucose values between two arbitrary set limits and frequency distribution of glucose levels [15]. However all these parameters have obvious limitations. The main drawback is the lack of information on either the size and number of glucose oscillations or the absence of discriminative power between major and minor oscillations. As a consequence, several other parameters were proposed for the assessment of glycaemic variability. The most used are:

- the mean of daily differences (MODD), i.e. the mean of the absolute differences between glucose values, calculated at the same time on two consecutive days [17];
- the mean amplitude of glycaemic excursions (MAGE) which is obtained by measuring the arithmetic mean of the differences between consecutive peaks and nadirs with measurement in the peak-to-nadir direction by the first qualifying excursion [14,15];
- the M value of Schlichtkrull et al. [18] which provides a measure of the stability of glucose metabolism in comparison with an arbitrary assigned ‘ideal’ glucose value;
- the S.D. of the mean around a mean glucose value [15].

At present, the MAGE seems to be the best method designed to quantify major swings of glycaemia and to exclude minor ones since its measurement implies that the differences between consecutive peaks or nadirs are only selected for the calculation when they are greater than the S.D. of mean glycaemic values [15]. However many physicians can be rebutted to use this technique that requires a continuous glucose monitoring. For that reason the new possibilities offered by the CGMS might be able to bring about a renewed interest for the assessment of MAGE in diabetes.

2.2. Do we have clear data indicating that glucose fluctuations play a role in diabetic complications?

For a long time it has been hypothesized that acute glucose swings might play an important role in the risk for long-term diabetic complications [19]. For instance, numerous pathophysiological studies have demonstrated that postprandial ‘hyperglycaemic spikes’ are accompanied by a series of alterations of coagulation and by an exaggerated production of free radicals [20]. As there are many reasons to think that the overproduction of superoxide by the mitochondrial electron-transport chain is one of the main mechanisms leading to an endothelial dysfunction and further to vascular damage [21,22], it is reasonable to suspect that PPG surges can favour the onset of or the progression to diabetic complications and as a consequence to consider that postprandial ‘hyperglycaemic spikes’ are ‘dangerous waves’ that exert deleterious effects on the vascular walls. Several epidemiological trials [23,24], follow-ups of cohorts [25,26] and meta-analysis [27] support this hypothesis. However at present we are still waiting for a long-term interventional trial specifically targeting PPG and proving, after several years of follow-up, a decreased risk for diabetic complications and cardiovascular events. As postprandial hyperglycaemia is the upward component of glucose swings, it is tempting to generalize the concept of ‘dangerous waves’ to both
upward and downward acute fluctuations of glucose around a mean value.

As above mentioned, in a study [12] involving patients with type 2 diabetes not using insulin, we found a strong positive linear correlation between the urinary excretion rates of isoprostanes, i.e. of metabolic products that are formed from free-radical-mediated oxidation of arachidonic acid, and the magnitude of glucose fluctuations as estimated from MAGE indexes. As the correlation with glucose fluctuations considered as a whole was stronger than that found with postprandial hyperglycaemia, we concluded that the upward and downward variations as observed during glucose swings amplify the triggering effect of the upward PPG spikes on oxidative stress. This finding may provide an explanation for some epidemiological observations of the DCCT. For example, in the subgroups with a sustained HbA1c of 9% for the entire study duration, the risk of retinopathy was reduced by more than 50% in the intensive control group compared with the conventional group, even though these two subgroups of patients had the same HbA1c [28]. The difference might be due to a lower intraday glucose variability in the intensive control group. However this hypothesis has not been confirmed by a recent analysis of the datasets collected in the DCCT. In a retrospective study, Kilpatrick et al. [16] reported that the mean blood glucose, i.e. sustained chronic hyperglycaemia, was predictive of microvascular complications in patients with type 1 diabetes while within-day glucose variability was not. However it should be noted that in this study the instability of blood glucose was calculated as the S.D. around the mean of a seven-point glycaemic profile measured at each patient’s quarterly visit. With such methodology the authors have probably selected not major fluctuations but rather a composite of both major and minor swings with a majority of minor ones. Furthermore Kilpatrick et al. [16] have probably blunted the contribution of major glucose fluctuations as it is not likely that the four pre-(inter-) prandial and the three PPG values included in the seven-point profile were in perfect coincidence with the nadirs and peaks of glucose, respectively. The following example should be useful to explain the superiority of the MAGE index for assessing the glucose variability compared with the S.D. of a seven-point glucose profile. Consider two patients with type 2 diabetes who have similar HbA1c and S.D. of glucose fluctuations around the mean. Assume that one subject has many minor glucose fluctuations and one or two major swings per day, while the other patient exhibits moderate glucose fluctuations over 24 hours. Despite similar S.D. of glucose around the mean, these two patients should exhibit very different MAGE values and thus Kilpatrick’s use of S.D. as a definitive measure of glucose variability is questionable. Even though the MAGE determination requires continuous glucose monitoring, our opinion is that this index should be the ‘gold standard’ for assessing glucose fluctuations in all prospective interventional trials designed to estimate glucose variability. Therefore expanded use of continuous glucose sensors [13] would be certainly useful for conducting such trials.

3. Continuous glucose monitoring in clinical practice: When? Whom?

3.1. A pedagogical tool in patients with type 2 diabetes

It is undoubted that absolute numbers and relative percentages of type 2 diabetic patients using insulin treatments will be increasing in the near future. This progression towards more insulin treatments results in part from the fact that more stringent recommendations have been made over the past years [29–31]. It is now well-recognized that type 2 diabetes is a progressive disease with a steady increase in HbA1c over time [32,33] and with a linear decline in the residual β-cell function [34,35]. Furthermore the life expectancy is getting longer and longer and, as a consequence, it can be predictable that the absolute number of type 2 diabetic patients who will reach a state of severe deterioration of the endogenous insulin secretion, several years from diagnosis, should be steadily increasing over the next years. Severe deterioration of insulin secretion is usually concomitant or synonymous of the so-called ‘oral antidiabetic drug secondary failure’, a state characterized by HbA1c levels above 8% even with maximal doses of OAD. For all these reasons, insulin treatments alone or in combination with OAD become recommended or even mandatory several years from diagnosis [36,37]. However, when patients do not achieve HbA1c levels < 7–8% despite multi-drug therapy with oral antidiabetic agents, initiation of insulin therapy is frequently delayed for several reasons. First, many physicians do not encourage their patients to switch to insulin treatment, because they are not familiar with the handling of insulin preparations and regimens. Second, the patients, themselves, have usually a poor perception of the insulin treatment that they consider as too complex with the risk for developing hypoglycaemia. All these factors contribute to inordinate long delays in the initiation of insulin treatments. As a consequence, even in developed countries, 10% is the usual average HbA1c level at which treatments are implemented in patients with type 2 diabetes [38,39].

One of the prerequisites for promoting earlier insulin treatment is to convince both general practitioners and patients that insulin therapy through its lowering effect on HbA1c levels is one of the best methods for preventing the onset of, or the progression to diabetic complications. However it remains surprising that even after years many patients are still unable to correctly interpret the meaning of their HbA1c [40]. By contrast, most patients have generally sufficient knowledge of their disease to be aware of what is considered a poor diabetic control in terms of blood glucose levels. As a consequence, patients who exhibit an unsatisfactory diabetic control, should be regularly tested for glucose concentrations at different time points by using SMBG [7]. This technique can act as a sensitizer to accept insulin treatment, especially when measurements are made at time points that correspond to glucose peaking. In this view, the mid-morning period is crucial since we have demonstrated that hyperglycaemia after breakfast is usually the highest postmeal glucose excursion over daytime [41].
Such a result was confirmed by using the CGMS [42] (Fig. 1). Moreover this technique is the only one that can provide a full picture of both postmeal surges and interprandial sustained hyperglycaemia in real life. The attainment of near normal glucose values at selected time points, usually at fasting, does not exclude abnormal peak and trough variations in glucose levels over postprandial or postabsorptive periods. The acute variations could remain totally ignored by both the patients and the medical practitioners in the absence of glucose monitoring over the periods of unsatisfactory glycaemic control. For that reason the expanded use of continuous glucose sensors is probably of interest to warn patients that their diabetic control is not as satisfactory as they believe and to incite them to accept an insulin therapy or more generally to accept a reinforcement of their therapeutic regimen. According to this clinical perspective, continuous blood glucose monitoring systems can serve as pedagogical tools for current clinical practice [43].

3.2. A monitoring tool for choosing insulin regimens and adjusting insulin doses in type 2 diabetic patients using insulin

At a first glance, the implementation of insulin treatment in type 2 diabetes could be considered as a simple process. Many authors have proposed to treat the insulin deficiency by using a basal insulin replacement therapy with a single injection of long-acting insulin analogue before dinner or at bedtime [44–46]. Such regimens associated with an oral therapy are generally sufficient for controlling the 24-hour post absorptive periods, i.e. the pre and interprandial glucose levels. Even though the pharmacokinetics and pharmacodynamics studies of long-acting insulin analogues indicate that some of them, more specifically glargine, exhibit a duration of action of 24 hours or more [47–49], basal insulin appears to be not able to control the blood glucose excursions over 24 hours in many patients. This could be due to at least two factors. The first one could be that basal insulins are not appropriate for controlling PPG surges and the second one could be that, in some patients, basal insulins are shorter lasting than expected [50]. This explains why some patients persist to exhibit HbA1c higher than 7% even when treat-to-target therapeutic strategies are implemented. The use of continuous glucose sensors is one of the ways to solve this problem. In many patients who do not achieve the targets it appears that postprandial excursions especially after breakfast remain abnormally high [51]. In this case, a better glycaemic control can be obtained by the incorporation of short-acting insulin injections, i.e. of prandial insulins before the meal that produces the largest PPG excursions [52]. Further injections can be gradually introduced at other pre-meal times as required. This provides a ‘step-by-step’ procedure towards an intensive basal-bolus therapy. The CGMS is probably a better tool for guiding such implementations than a self-blood glucose monitoring using a several-point discontinuous profile. In a previous unpublished trial we have used the continuous blood glucose system for assessing the efficiency of a single prebreakfast injection of a rapid insulin analogue (Aspart) in six poorly controlled type 2 diabetic patients (median HbA1c = 9.85%, range 7.9–11.4%) who were treated by maximal doses of OAD. After 3 months of therapy, we observed a significant (P = 0.046) improvement in HbA1c levels (median = 7.85%, range 7.3–8.7%). However the most interesting finding was the change observed in the continuous glucose profile over daytime (Fig. 2). As expected postbreakfast excursions were blunted by the prandial insulin shot of Aspart but the unexpected result was the observation of a prolonged improvement in glucose concentrations over the postlunch period up to dinner time. This apparently surprising result confirms that any glucose concentration at a given time point is always dependent on the glucose values that precede it. In other words, improvements in postbreakfast glucose result in reductions of the subsequent prelunch and postlunch glucose values. Even though this study was performed in a limited number of patients, the data suggest that prebreakfast bolus of short-acting insulin analogues might be useful for patients who are already treated with a once-daily basal insulin injection and who do not reach the targets especially over the morning period. Such insulin regimens that contain once-daily injection of basal insulin at dinner and once-daily bolus of prandial insulin at breakfast would be certainly better implemented if based on the analysis of a continuous glucose profile.

![Glucose concentration (mg/dL)](image1)

**Fig. 1.** Continuous glucose monitoring in 24 non-insulin-using type 2 diabetic patients (HbA1c, range from 7.3% to 9.2%). The postbreakfast period is indicated by the shaded area.

![Glucose concentrations (mg/dL)](image2)

**Fig. 2.** Continuous glucose monitoring in six non-insulin-using type 2 diabetic patients before and 3 months after the initiation of a treatment with a single prebreakfast bolus of insulin Aspart (unpublished data).
4. Conclusion

Even though the exact indication of continuous glucose sensors has to be better defined in type 2 diabetes, our opinion is that their use should increase over the next years both for research purposes and more prosaically for current clinical practice as it has been suggested in patients with type 1 diabetes [53]. In research trials the continuous glucose systems are the only methods that permit to precisely assess the relationship between glucose variability and vascular damages. In clinical practice, continuous glucose monitoring is certainly a tool that should be useful for improving the patient’s knowledge of their disease, and thus for implementing insulin treatments, earlier and better in insulin-requiring type 2 diabetic patients.

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References


