Advances in Understanding Glucose Variability and the Role of Continuous Glucose Monitoring

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Abstract

Recent data have suggested that glucose variability may add to or modify the risk of diabetes complications. Glycated haemoglobin (HbA_{1c}), an integrated measure of sustained chronic hyperglycaemia, fails to reflect glucose variability and the risks associated with extreme glucose swings. Thus, whether glucose variability should become an integral part of assessing glucose control in clinical practice remains unknown. Since the establishment of continuous glucose monitoring (CGM) systems, various indices of glucose variability and quality of glycaemic control such as the mean amplitude of glycaemic excursions (MAGE) and the Glycaemic Risk Assessment Diabetes Equation (GRADE) can now be precisely computed from CGM data sets. Analysis of CGM data, including the impact of glucose variability and its temporal aspects, has clinical importance and should be incorporated into use in clinical trials and the design of optimal antidiabetes therapies.

Evidence from several large randomised clinical trials has linked glycated haemoglobin (HbA_{1c}) to vascular diabetes complications.[1,2] Consequently, current diabetes management relies mainly on HbA_{1c} to assess quality of treatment and to adjust therapy. Optimal glycaemic control aims to restore levels of HbA_{1c} to as normal as possible to reduce or avoid diabetic complications. However, traditional glucose monitoring has considerable limitations in assessing glycaemic control due to inability to detect fluctuations in glucose levels. Continuous glucose monitoring (CGM) systems allow the detection of the configuration of glucose patterns in several metabolic conditions. Analysis of the CGM patterns revealed that in a portion of patients with diabetes the same HbA_{1c} level may generate unpredictable diurnal glucose fluctuations with different magnitudes.[3] As low glucose levels often offset the high glucose levels, even patients with HbA_{1c} levels within the target range (<6.5%) show remarkable glucose fluctuations.[4] Thus, HbA_{1c} fails to reflect glucose variability, i.e. the large downward and upward swings in glucose levels during hypoglycaemia and post-prandial periods, respectively. The clinically most important manifestations of glucose variability are elevated post-prandial glucose excursions and hypoglycaemia. Particularly in type 1 diabetes, often glucose variability triggers hypoglycaemia, and data have linked large glucose excursions to the risk of multiple episodes of hypoglycaemia. Although a growing body of evidence suggests that, in addition to and independently of HbA_{1c}, glucose variability may play an important part in the development of diabetes complications, conclusive data from long-term randomised trials have yet to be published. This report discusses the evaluation of glucose variability, focusing on CGM technology, its associations with metabolic characteristics and possible implications for glycaemic control.

Quantification of Glucose Variability and Quality of Glycaemic Control

Indices of Glucose Variability

Assessing difficult metabolic situations requires detailed information about the degree of instability for optimal adjustment of therapy. Glucose variability is estimated by computing characteristic indices from glucose profiles. In the past, intermittent blood glucose monitoring was mainly used for constructing such glycaemic profiles. However, despite frequent measurements, traditional monitoring does not provide the information required on glucose fluctuations. Using CGM, several indices can be estimated and proposed for the quantification of glucose variability.

One simple measure of glucose variability is the standard deviation (SD) around the mean glucose value. However, this index gives a dispersion of all glucose measurements, is sensitive to outliers and the same numerical values can have differing glycaemic patterns. We recently developed computer software (unpublished) that provides mean glucose profiles from CGM modal day plots on a single timescale and the overall SD around the mean (see *Figure 1*). Periods of lower and higher glucose variability are easily discerned, improving the evaluation of glycaemic control and allowing appropriate

Figure 1: Computerised Analysis of a Continuous Glucose Monitoring Modal Day Plot Showing Mean Glucose Values and Standard Deviation
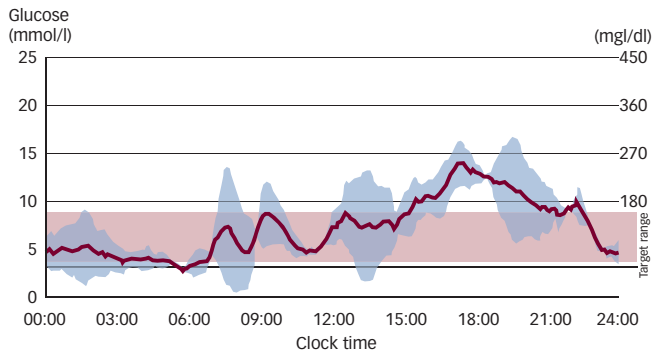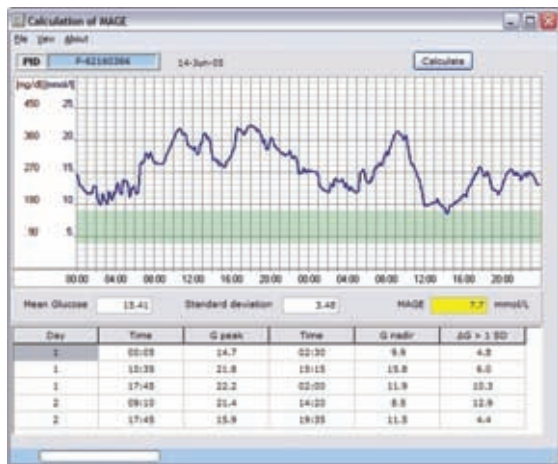

Figure 2: Computerised Calculation of Mean Amplitude of Glycaemic Excursions for a Patient with Type 2 Diabetes

The continuous glucose monitoring (CGM) profile of two successive 24-hour periods is shown. The mean values (mmol/l) for glucose (G), standard deviation (SD) and mean amplitude of glycaemic excursions (MAGE) are indicated (boxes). The day, time-point of glucose peaks and nadirs and the difference peak-to-nadir and nadir-to-peak (Δg), respectively, are given in the table (bottom).

therapeutic intervention. In addition, several subtypes of SD have been described, as well as methods for their calculation.[5]

The mean amplitude of glycaemic excursions (MAGE)[6] selects the major glucose swings and represents the arithmetic mean of the difference between consecutive glucose increases or decreases exceeding one SD around the respective mean 24-hour glucose value. Thus, the MAGE only incorporates data from large excursions and ignores the majority of values of the glucose profiles. Although reasonable, the qualifying limit of one SD is arbitrary, and minor imprecisions may have substantial consequences for results. Furthermore, high MAGE readings will result if only one major upward or downward glucose swing occurs during two consecutive 24-hour periods. In order to exclude largely operator-dependent influences when a graphical approach is used, we have developed computer software for calculating MAGE values from CGM system measurements (unpublished) with the criterion that glucose excursions exceed one SD of the arithmetic mean of two successive 24-hour periods, as illustrated in *Figure 2*.

The interquartile range (IQR)[7] and sensor glucose range (SGR; glucose maximum to glucose minimum) may also be utilised as indices of glucose variability. Newer indices such as the continuous overall net glycaemic action (CONGA),[8] which reflects the SD of the difference in glucose levels using different time windows, and the lability index (LI)[9] have also been used for estimation of glycaemic variability. However, some indices differ in their proportion of greater emphasis of either hypoglycaemia or hyperglycaemia. MAGE emphasises hyperglycaemia due to meals. LI correlates well with the clinical assessment of glucose lability but may not provide sufficient weight to the degree of hyperglycaemia. CONGA, as an index to measure intra-day glucose variability within defined time windows, may be specifically used in cases in which glucose control is critical and needs therapeutic adjustment. As yet, no single index functions as the 'gold standard' for assessing glycaemic variability and interpreting CGM data. From a practical point of view, the SD score is a simple, reproducible index that can be easily computed from CGM data sets, as suggested above (see *Figure 1*). MAGE may become the standard for assessment in type 2 diabetes because of the magnitude of post-prandial hyperglycaemic excursions and their suggested association with cardiovascular complications.[10]

Indices of Quality of Glycaemic Control

In addition to evaluation of glucose variability, various indices have been developed to estimate the quality of glycaemic control to complement clinical assessment of diabetes treatment, such as the average daily risk range (ADRR), including the high (HBGI) and low blood glucose index (LBGI),[11] the index of glycaemic control (IGC)[5] and the glycaemic risk assessment diabetes equation (GRADE).[12] These measures quantify the risk for glycaemic extremes in addition to describing temporal aspects of glucose fluctuations.

As ADRR and GRADE, for example, include both hyper- and hypoglycaemia, these quality indices may preferably be used to quantify glycaemic control in type 1 diabetes, in which the problem of hypoglycaemia is considerable. However, any index used to assess glucose variability or quality of glycaemic control should be based on glucose level fluctuations during a time period that is representative and sufficiently long for accurate computing. These time periods differ among the indices, ranging from five days for the SD score and MAGE to eight days for LI and GRADE.[13] The time periods also depend on whether CGM was performed blinded or unblinded, using retrospective or realtime CGM systems. Complexity measures, e.g. de-trended fluctuation analysis (DFA),[14] may have some advantages over the above-mentioned indices to explore gluco-regulatory responses in subjects with progressing impairment of glucose tolerance.

In view of the large data output from CGM, it is necessary to have a minimum of meaningful estimates for the assessment of diabetes control in clinical practice. Based on our experience, we recommend the parameters listed in *Table 1* as measures for overall glycaemic control in addition to the long-term HbA$_{1c}$ measure. Since the indices of glucose variability are intercorrelated[5] in most cases, estimation of one of these indices is sufficient.

Associations of Glucose Variability with Measures of Glycaemic Control and Beta-cell Function

Regardless of which variability index is used to assess glucose fluctuations, all indices correlate either weakly or not at all with HbA$_{1c}$,[3,15] giving further support to the notion that glucose variability and HbA$_{1c}$ are different measures of diabetes control. Using simple

correlation analysis, *Table 2* shows the associations of conventional measures of glycaemic control and CGM measures with some indices of glucose variability in a cohort of 114 continuously monitored patients with type 2 diabetes (aged 64±8 years, diabetes duration 7±5.7 years, body mass index 30.8±4.2kg/m², HbA$_{1c}$ 6.8±1.1%; means ± SD). Weak correlations between HbA$_{1c}$ and the indices of glucose variability are shown, whereas all other measures of glycaemic control, except duration of hypoglycaemia, show markedly stronger correlations.

The progressive loss of glucoregulation and stability of diabetes is reflected by an increasing frequency and height of the amplitude of glucose excursions. Although several factors might be involved in this process, diabetes instability has been shown to parallel the insulin reserve and secretory capacity.[16] In type 1 diabetes the insulin reserve is absent, while in type 2 diabetes a gradual exhaustion occurs, depending largely on the degree of insulin resistance and disease duration. The relationship between beta-cell function and glucose variability becomes apparent on comparison of variability indices in type 1 diabetes and in various segments of patients with type 2 diabetes using oral hypoglycaemic agents (OHAs) and insulin either alone or in combination. *Figure 3* shows an example of how the MAGE index, when going from type 2 to type 1 diabetes, rises continuously with declining beta-cell reserve, and thus with the need for exogenous insulin.

Indeed, a strong non-linear association was observed between glucose variability (MAGE) and post-prandial beta-cell function in the segment of OHA users (r=0.54; p<0.001). A similar relationship, although weaker, was also found between MAGE and the basal beta-cell function (r=0.39; p=0.025).[17] Interestingly, MAGE did not correlate with insulin sensitivity and fasting insulin or post-prandial insulin levels.

Glucose Variability and Improvement of Glycaemic Control

The quality of glycaemic control and adjustment of diabetes therapy are primarily based on evaluation of HbA$_{1c}$ levels, as HbA$_{1c}$ often represents the only measure of glycaemic control in routine diabetes management. One frequent consequence of reducing HbA$_{1c}$ to achieve target levels is an increased number of hypoglycaemic episodes, which may have an unfavourable outcome – especially in patients of higher age and with longer disease duration.[18] Without CGM, the frequency, magnitude and duration of blood glucose fluctuations remain undetected.

Pramlintide diminishes gastric emptying, reduces elevated plasma glucagon, improves overall glycaemic control and attenuates glucose fluctuation. A recent study in patients with type 1 diabetes showed that addition of pramlintide to insulin therapy reduced the rate and magnitude of post-prandial glucose excursions without increasing the risk of hypoglycaemia.[19]

In paediatric patients with type 1 diabetes on a multiple daily injection (MDI) regimen, treatment with insulin glargine, as the basal component, significantly reduced glucose variability as measured by SD score, M-value and MAGE, whereas neutral protamine Hagedorn (NPH)/Lente insulin reductions were not significant.[20] Continuous subcutaneous insulin infusion (CSII) was even more effective at reducing glucose variability than MDI.[21] These data again demonstrate that restoration towards the normal pattern of glucose fluctuations by providing insulin in a more physiological manner results in improved glycaemic control and higher treatment satisfaction.

Table 1: Parameters Derived from Continuous Glucose Measurements for Evaluation of the Overall Quality of Glycaemic Control

| Quality of Glycaemic Control |
| --- |
| Mean glucose |
| Duration of hyperglycaemia |
| Duration of hypoglycaemia |
| Hyperglycaemic episodes |
| Hypoglycaemic episodes |
| **Glucose Variability** |
| SD score |
| Sensor glucose range |
| IQR |
| MAGE |
| CONGA |

CONGA = continuous overall net glycaemic action; IQR = interquartile range; MAGE = mean amplitude of glycaemic excursions; SD = standard deviation.

Table 2: Correlation Between Measures of Glycaemia and Indices of Glucose Variabilty and Quality of Diabetes Control

Measures of Glycaemic Control	SD Score	IQR	Sensor Range	MAGE	ADRR
HbA$_{1c}$	0.34	0.31	0.21	0.26	0.24
Mean glucose	0.49	0.52	0.43	0.51	0.26
Fasting glucose	0.39	0.46	0.31	0.45	0.32
Post-prandial glucose	0.48	0.53	0.41	0.51	0.43
Duration of hyperglycaemia (>10mmol/l)	0.72	0.72	0.62	0.68	0.49
Duration of hypoglycaemia (<3.3mmol/l)	0.16	0.07	0.13	0.07	0.36

At this sample size, correlations >0.3 are significant at p=0.001. Correlations <0.2 are not significant. ADRR = average daily risk range; HbA$_{1c}$ = glycated haemoglobin; IQR = inter-quartile range; MAGE = mean amplitude of glycaemic excursions; SD = standard deviation.

Figure 3: Increase of Glucose Variability as Measured by Mean Amplitude of Glycaemic Excursions Index in Relation to Insulin Requirement for Diabetes Control
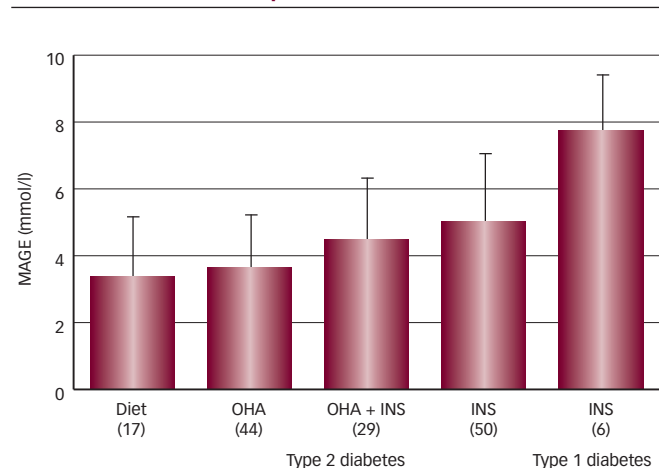
INS = insulin; MAGE = mean amplitude of glycaemic excursions; OHA = oral hypoglycaemic agents.

The incretin mimetic exenatide is a powerful agent that potentiates post-prandial insulin release and stimulates beta-cell growth.[22] When used adjunctively in patients with type 2 diabetes sub-optimally controlled with OHA, exenatide reduced the overall risk of glycaemic

variability (ADRR) and glucose extremes to a greater extent than insulin glargine at similar average glycaemia.[23] Thus, decreased glycaemic variability may represent an improved outcome and better quality of life, even in cases where HbA$_{1c}$ is not significantly reduced.

Glucose variability has recently emerged as an independent predictor of intensive care unit (ICU) and hospital mortality.[24] Even a modest degree of hyperglycaemia occurring after ICU admission was associated with a substantial increase in hospital mortality.[25] The odds ratio associated with glucose variability and that associated with mean blood glucose levels were comparable in terms of predicting mortality.[26] Interestingly, the association between glucose variability and mortality was strongest in the euglycaemic range.

Mortality increased from 5.9% in the lowest quartile up to 37.8% in the highest quartile of glucose variability.[24] The data strongly suggest that increasing glucose variability confers a strong independent risk of mortality in critically ill patients. Estimation of glucose variability should thus be taken into account in future investigations in glucose monitoring in critically ill patients. Current glucose monitoring technology using subcutaneous sensors still appears inadequate for critical care patients requiring intensive insulin therapy.

Glucose Variability and Diabetes Complications

Several *in vitro* studies have previously shown that exposure of cell cultures to rapid glucose fluctuations produced more severe cellular damage than exposure to sustained hyperglycaemia.[27,28] These observations are consistent with *in vivo* studies that demonstrated that hyperglycaemic spikes induced oxidative stress and increased production of various mediators of inflammation, leading to dysfunction of both vascular endothelium and pancreatic beta cells.[29,30] Oxidative stress thus likely plays a significant role in the pathogenesis of diabetic complications.

Monnier et al.[31] used CGM measurements in patients with type 2 diabetes and found a close association between markers of oxidative stress and the MAGE index; no such relationship was found with markers of chronic sustained hyperglycaemia. This supports the currently debated argument that glucose fluctuations are more important than sustained chronic hyperglycaemia in the development of secondary diabetes complications, primarily in type 2 diabetes.[10,32] It is somewhat surprising and difficult to explain that such a relationship between glucose variability and elevated levels of oxidative stress could not be confirmed in patients with type 1 diabetes.[33]

Soluble adhesion molecules are in fact well-known predictors of cardiovascular disease.[34] The finding of increased soluble P-selectin levels in patients with type 2 diabetes with glucose instability[35] indicates the involvement of glucose fluctuations in the dysfunction of vascular endothelial cells. Evaluation of hard clinical end-points in prospective analyses further revealed that glucose excursions during post-prandial times are strong predictors of retinopathy[36] and cardiovascular events.[37,38] In light of current data, it is clear that glucose variability can no longer be ignored as an important factor in glycaemic control.[39] However, to definitively conclude that reduction of glucose variability can reduce the risk of vascular complications in diabetes and the increased mortality in critically ill patients, randomised long-term clinical trials using CGM technology and standardised measures for glucose variability must be performed.

Conclusion

The application of CGM systems in patients under ambulatory and fed conditions allows the assessment of individual glucose patterns in type 1 and type 2 diabetes. Analysis of the glucose dynamics reveals remarkable glucose fluctuations, even with HbA$_{1c}$ levels within the target range. In view of accumulating data that glucose variability represents an independent factor for micro- and macrovascular complications, standardised estimates of glucose variability and the quality of glycaemic control are of clinical importance. A number of indices have been proposed to assess glycaemic control. Because of the information density, CGM data sets provide a unique opportunity to calculate these indices using appropriate computer software. Although there has not yet been consensus as to which of the indices should be used in clinical practice, we propose SD score or IQR and MAGE to measure glucose variability and GRADE to assess the quality of glycaemic control, but additional indices may be computed from CGM data. The use of these indices in conjunction with HbA$_{1c}$ will significantly contribute to the improvement of current glycaemic management. To conclusively determine whether reduction of glucose variability reduces the risk of late diabetes complications or mortality in critically ill patients, randomised clinical trials using CGM must be performed along with a systematic approach to evaluating these data. ■

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