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Glycaemic Variability: Its Clinical Implications And Management

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ABSTRACT

Glycaemic control and its benefits in preventing microvascular diabetic complications are proved by various studies. Diabetes control and complications trial (DCCT) had reported variable glycated haemoglobin (HbA1c) as a cause of increased microvascular complications in conventional glycaemic control group versus intensive one. However, in spite of several indirect evidences, its link with cardiovascular events or macrovascular complications is still not proved beyond doubt. Glycaemic variability (GV) is one more tool to explain relation between hyperglycaemia and increased cardiovascular risk in these populations. Studies on the cellular level and in humans have shown a correlation between increased GV and oxidative stress and endothelial dysfunction. GV is significantly associated with morbidity and mortality of critically ill people.

INTRODUCTION

Swings in blood glucose level are known as glycaemic variability. Diminished glycaemic auto-regulation or short falls of insulin availability are thought to be the etiological factors for these glycaemic bumps. Intermittent high blood glucose level has more detrimental effect than constantly high blood glucose level as shown in different studies.[1-5] When we target for optimum glycaemic control, it is also become important to focus on glycaemic variability as an additional goal point along with the traditionally followed parameters.

GLYCAEMIC VARIABILITY: DEFINITION

Glycaemic variability is defined as the intraday glycaemic excursions including episodes of hyper- and hypoglycaemia. The postprandial hyperglycaemia excursions also contribute to glycaemic variability. The presence of various microvascular and macrovascular complications in diabetes is contributed by dysglycaemia (peaks and nadirs).[6-9]

IMPORTANCE OF GLYCAEMIC VARIABILITY AND HbA1C

Glycated haemoglobin variability was proposed to explain the development of retinopathy and nephropathy in conventional group.[10] The positive association with cardiovascular risk factors supports the possibility of relationship between glucose variability and cardiovascular morbidity and mortality. Most studies have shown strongest correlations between A1c and mean plasma glucose levels and it is recognized as reliable marker in glycaemic stability and its direct consequence.[11-13] A1c is an integrator of both fasting and postprandial glycaemic disorders. As a consequence, it is not surprising that fasting and postprandial hyperglycaemia were identified separately or concomitantly as major risk factors for diabetes complications.

METRICS OF GLYCAEMIC VARIABILITY

Glycaemic variability is usually defined by the determination of fluctuations of glucose or other related parameters of glucose homoeostasis over a certain interval of time. This description covers two predominant categories of measurements (Table 1): short-term glycaemic variability, represented by both within-day and between day glycaemic variability, and long-term glycaemic variability, based on serial measurements over a longer period of time, involving HbA1c predominantly, but sometimes serial fasting plasma glucose (FPG) and postprandial glucose (PPG) measurements. For many years, short-term glycaemic variability was calculated from self-monitoring of blood glucose (SMBG) measurements,[14] but this method has been progressively replaced over the past few years by continuous glucose monitoring (CGM).[15,16] SMBG, at best, provides an abbreviated diurnal blood glucose profile,[17] whereas CGM, with interstitial glucose measurements at 5 min intervals, provides a more comprehensive record, covering both day and night, and is regarded as the gold standard method for assessment of short-term glycaemic variability.[15,16] Fleisher and colleagues[17] also reported a poor correlation (R^2=0·26, p<0·05) between the mean amplitude of glycaemic excursion (MAGE) obtained from structured SMBG testing and MAGE computed from CGM. However, structured SMBG can be used to determine the two main components of short-term glycaemic variability, i.e., the within-day and between-day glycaemic variability.

MAIN METRICS OF GLYCAEMIC VARIABILITY

The metric appears to be the best for estimating the between-day glycaemic variability is the mean of daily differences (MODD),[18] which was introduced in the early 1970s by Molnar and colleagues.[19] High MODD score is indicative of large between-day glycaemic variability. This metric cannot be measured with available CGM devices and thus requires additional computation. Other more complex metrics are also available to assess short-term glycaemic variability, but are rarely applied in routine clinical practice.

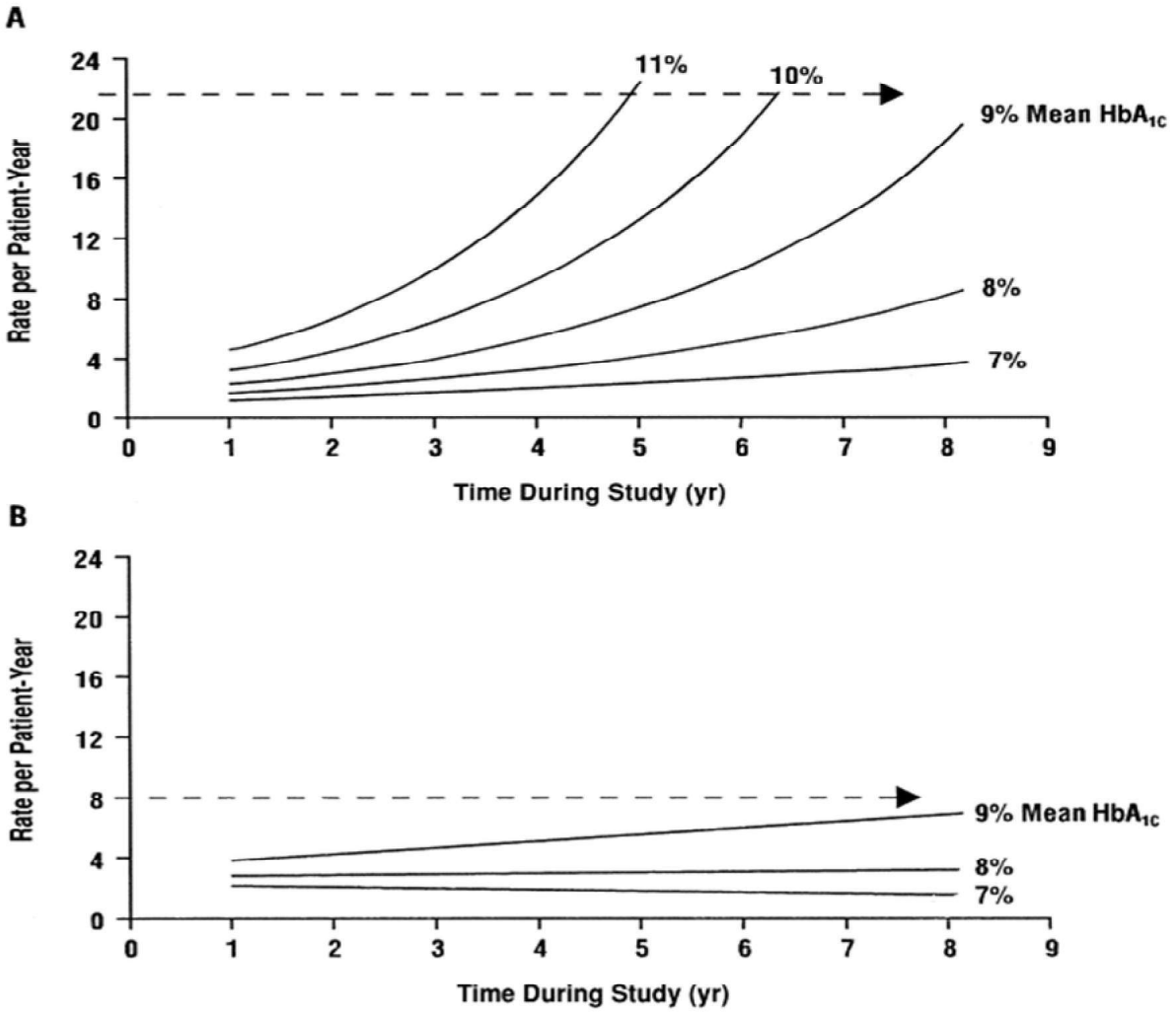
The second type of glycaemic variability, namely long-term glycaemic variability, is usually based on clinic measurements of HbA1c, FPG, or PPG,[20] with the subsequent calculation of their standard deviation (SD) and coefficient of variation (CV). Long-term glycaemic variability is partly a reflection of ambient hyperglycaemia because measures of long-term variability correlate with either mean concentration of blood glucose (r=0·73) or mean HbA1c (r=0·55).[10] This definition of long-term variability is likely to be a generic term that encompasses different concepts and definitions (Table 1).[21]

CGM: continuous glucose monitoring; CONGA: continuous overall net glycaemic action; CV: coefficient of variation; MAGE: mean amplitude of glycaemic excursion; MODD: mean of daily differences; SD: standard deviation; SMBG: self-monitoring of blood glucose. Units are in mmol/L or mg/dL depending on the unity of the glucose values measured. To convert glucose values from mg/dL to mmol/L multiply by 0.0555.

Table 1: Metrics of glycaemic variability.

Variability measure	Formula	Explanation of symbols	Discriminating feature
SD	$\sqrt{\frac{\sum(x_i-\bar{x})^2}{k-1}}$	x_i = individual observation $\bar{x}$ = mean of observations k = number of observations	easy to determine, extensively used
CV	$\frac{s}{\bar{x}}$	s = standard deviation $\bar{x}$ = mean of observations	easy to determine, SD corrected for mean
adjusted M-value	$M_{GR}+M_W$ where $M_{GR}=\frac{\sum_{i=t_1}^{t_n}\left\|^{10}\log\frac{GR_i}{IGV}\right\|^3}{n}$ and $M_W=\frac{G_{max}-G_{min}}{20}$	M_{GR} = M-value for glucose readings M_W = correction factor for n <24 GR_i = glucose reading at time t IGV = ideal glucose value t_i = time in minutes after start of observations of the i^{th} observation G_{max} = maximum glucose reading G_{min} = minimum glucose reading	not a pure variability measure
MAGE	$\sum\frac{\lambda}{n}$ if $\lambda > v$	λ = each blood glucose increase or decrease (nadir-peak or peak nadir) n = number of observations v = 1 SD of mean glucose for 24-hr period	used most extensively
CONGA	$\sqrt{\frac{\sum_{t=t_1}^{t_{k^*}}(D_t-\bar{D})^2}{k^*-1}}$ where $D_t=GR_t-GR_{t-m}$ and $\bar{D}=\frac{\sum_{t=t_1}^{t_{k^*}}D_t}{k^*}$	k^* = number of observations where there is an observation n x 60 minutes ago $m=n\times60$ D_t = difference between glucose reading at time t and t minus n hours ago	specifically developed for CGM
MODD	$\frac{\sum_{t=t_1}^{t_{k^*}}\left\|GR_t-GR_{t-1440}\right\|}{k^*}$		inter-day variation

Source: Adapted from Siegelaar SE, Holleman F, Hoekstra JB, et al. Glucose variability; does it matter. Endocrine Reviews. 2010;31:171-82.



Figs. 1A and B: *Same HbA1c but different results with glycaemic variability (GV).*

Source: Adapted from Kilpatrick ES, Rigby AS, Atkin SL. Effect of glucose variability on the long-term risk of microvascular complications in type 1 diabetes. Diabetes Care. 2009;32:1901-3.

Same HbA1c but different results with glycaemic variability in shown in Figure 1.

The lack of consensus on the metrics to connote both short-term and long-term glycaemic variability partly contributes to difficulties in establishing the relations between these measures and actual clinical outcomes.

BIOCHEMISTRY OF GLYCAEMIC VARIABILITY AND OXIDATIVE STRESS (FIG. 2)

There is overproduction of superoxide by the mitochondrial electron-transfer chain and in turn production of cascade of deleterious effects as enhanced polyol activity, increased generation of advanced glycation end products, activation of protein kinase C (PKC) and nuclear factor-kB and increased hexosamine pathway flux. Via these pathways, increased intracellular reactive oxygen species (ROSs) lead to defective angiogenesis in response to ischaemia, activate a number of proinflammatory pathways, and produce long-lasting epigenetic changes that drive persistent expression of proinflammatory genes after glycaemia is normalized ("hyperglycaemic memory").[22] In a study by Quagliaro et al. involving human umbilical vein endothelial cells exposure to intermittent raised glucose versus exposure to stable high glucose environment, observation was apoptosis of endothelial cells exposed to intermittent high glucose.

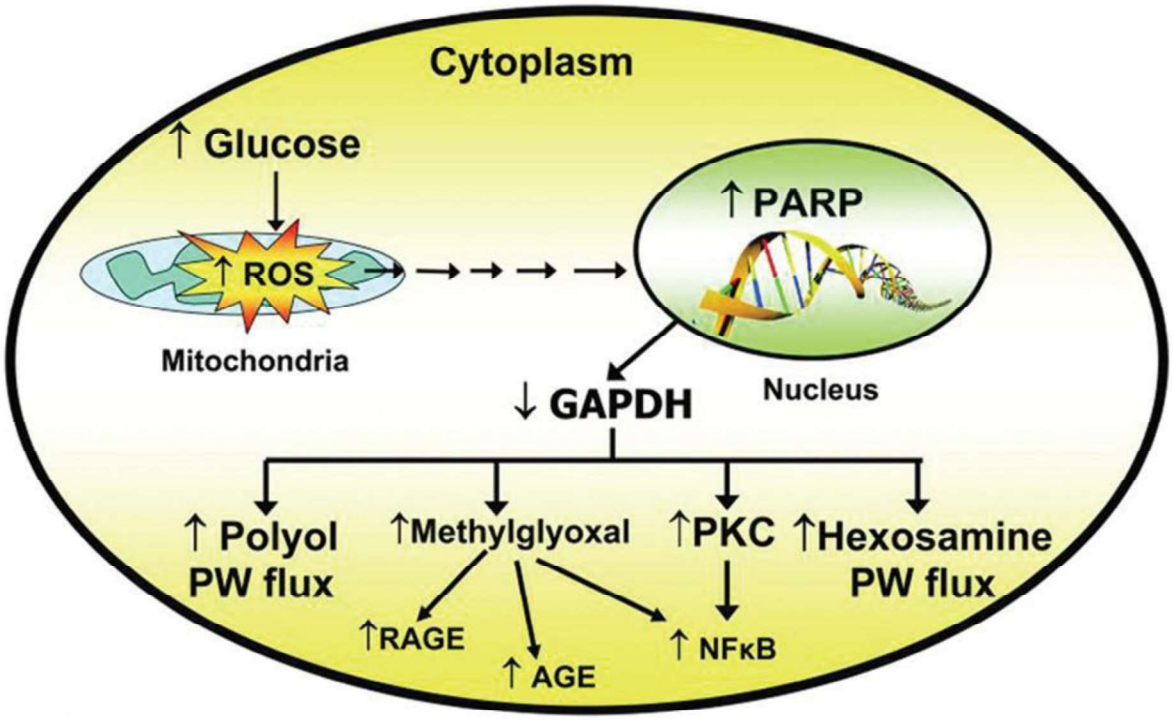


Fig. 2: Pathophysiological mechanism of hyperglycaemia-induced cellular damage mediated by oxidative stress.

Source: Adapted from Giacco F, Brownlee M. Oxidative stress and diabetic complications. Circ Res. 2010;107:1058-70.

This may be related to ROS overproduction, through PKC-dependent activation of nicotinamide-adenine dinucleotide phosphate (NADPH)-oxidase.

ROS: reactive oxygen species; PARP: polyadenosyl ribose phosphate; GAPDH: glyceraldehyde 3-phosphate dehydrogenase; PKC: protein kinase C; NF and #954; B-nuclear factor kappa B; AGE: advanced glycation end products; RAGE: receptor for advanced glycation end products; PW: pathway

GLUCOSE VARIABILITY AND CLINICAL OUTCOMES IN PEOPLE WITH OR WITHOUT DIABETES

Before 2015, several studies had depicted a positive association between glycaemic variability and complications of diabetes, both macrovascular and microvascular.[23] Since 2015, new evidence has also surfaced in support of glycaemic variability as an independent risk factor for total mortality and death due to cardiovascular disease (CVD) in both type 1 and type 2 diabetes.[20,24-28]

Notably, glycaemic variability also seems to have an effect in people without diabetes. It is has been reported as a risk factor for a worse outcome in several acute conditions,[29] although, when corrected for other confounding variables, this association can be lost.[30]

GLYCAEMIC VARIABILITY AND HYPOGLYCAEMIA

In DCCT trial 10–30% incidence of hypoglycaemia was observed in intensive insulin receiving group. Hypoglycaemia was the main accompanying complication when desired glucose target was intensively achieved. The frequency of severe hypoglycaemia increases exponentially when lowering blood glucose[31] and several studies have reported that low glucose variability coincided with decreased incidence of hypoglycaemia.[32] Glucose variability was mentioned as measure of predictor of future severe hypoglycaemia than HbA1c by Cox et al.[33] In a study by Kilpatrick et al. using datasets of the DCCT found that glucose variability, calculated as SD of SMB and MAGE as an independent predictor of hypoglycaemia just like MBG and other study.

GLYCAEMIC VARIABILITY AND DIABETIC MICROVASCULAR COMPLICATIONS

Bragd et al. found that glycaemic variability was an independent predictor of the prevalence of peripheral neuropathy, however, no significant relationship was observed between glycaemic variability and the development of other microvascular complications such as retinopathy or nephropathy in the cohort.[34] Additionally, glycaemic variability was borderline predictor of incidence of peripheral neuropathy, suggesting the association of neuronal damage with glycaemic variability.

GLYCAEMIC VARIABILITY AND CARDIOVASCULAR HEALTH

The analysis of DCCT data by Kilpatrick et al. showed that pre- and postprandial blood glucose (PPBG), MBG were significantly related to CVD risk. However, there was no relation between HbA1c and glucose variability. They followed type 1 diabetes patients during a 9-year period in which pre-and postprandial 7-point glucose profiles were taken quarterly and used to calculate measures of glycaemic control including MBG, HbA1c, and within-day SDBG.[35]

In a study by Gordin et al., in type 1 diabetic patients, daily glucose variability was assessed against arterial stiffness as a marker of effects of blood pressure, an early sign of macrovascular disease. Glucose variability was measured by MAGE. It was found that arterial stiffness was correlated to MBG not the MAGE. However, glycaemic variability was positively associated with changes in systolic and diastolic blood pressure.[36,37]

In multivariate analyses, glucose peak was a significant independent determinant of carotid intima-media thickness (CIMT) and explained 49% of the variability.[38] In a recent study of type 2 diabetes mellitus with stroke, PPBG was significantly associated with CIMT and stroke.[39]

GLYCAEMIC VARIABILITY AND QUALITY OF LIFE

Frequent fluctuations in blood glucose with hypoglycaemia and glycaemic excursions negatively affect individuals' mood changes with deterioration of diabetic complications, depression and low quality of life. Large glycaemic variability was found to be associated with poor quality of life than HbA1c and 24 h average blood glucose.[40]

MANAGEMENT OF GLYCAEMIC VARIABILITY

Lifestyle Measures

Weight loss significantly improved not only insulin sensitivity but also beta-cell function, able to reduce glucose levels and delay the progression from impaired glucose tolerance (IGT) to diabetes.[41,42] Recently a research study on diet of high glycaemic meal with pistachio nuts has shown diminished postprandial response. The study assessed glucose and insulin responses over 3 h, as well as glucose-dependent insulinotropic peptide and glucagons-like-peptide-1 and ghrelin.

Role of Drugs

Oral Hypoglycaemic Agents

In continuous interstitial glucose sensor monitoring system (CGMS) measures of glucose intraday variability, MAGE, SD, mean glucose levels, CONGA and interday variability, MODD were observed to be significantly reduced when treated with acarbose in a 16-week intention-to-treat study with glibenclamide in combination with metformin although the overall glucose level did not differ much.[43] Bao et al.[44] showed that efficacy of controlled-release glipizide combined with acarbose was more in reducing MAGE than controlled-release glipizide monotherapy.

Glimepiride on pharmacogenomic basis should cause less glycaemic variability than glibenclamide. Extra pancreatic effect, rapid association, and dissociation binding properties with receptors and effect on both phases of insulin secretion in patients with type 2 diabetes are usually sought.[45,46]

Prandial Insulins

There is attenuation and progressive delay of

prandial insulin response contributing to increasing hyperglycaemia in established type 2 diabetes. Over and above due to longer duration of action, inter meal hypoglycaemia is quite frequent with regular insulin. Newer rapid prandial insulin analogue are rapidly absorbed and their action closely mimics the normal physiological insulin response to meals.

Basal Insulins

In LANMET[47] study, the mean A1c level dropped by 2% from base line to endpoint, it was commented by Monnier et al. that glucose variability remained unchanged, and addition of a bed time insulin dose failed to modify the acute glycaemic variability from peaks to nadirs, whatever the type of insulin used.

In the DEVOTE trial,[48] the cardiovascular safety of insulin degludec was compared with insulin glargine 100 U/mL in patients with type 2 diabetes at high cardiovascular risk. The treatments led to similar glycaemic control (HbA1c) and degludec was non-inferior to glargine with respect to the primary cardiovascular outcome. Notably, insulin degludec lowered episodes of confirmed severe hypoglycaemia by 40% and nocturnal severe hypoglycaemia by 53%.

Basal bolus insulin therapy and GLP 1 receptor agonist therapy:

When basal insulin supplementation is deemed inadequate in type 2 diabetes, two further options are available: the addition of a GLP-1 receptor agonist or a short-acting insulin analogue. There are two randomised studies, the FLAT-SUGAR trial[49] and the AWARD-4 sub-study,[50] that have assessed the effect of basal insulin in combination with a GLP-1 receptor agonist on both ambient hyperglycaemia and glycaemic variability. The FLAT-SUGAR trial was a 26-week randomised trial comparing a basal-bolus insulin regimen with basal insulin and the short-acting GLP-1 receptor agonist exenatide, injected twice daily before the largest meals. This therapeutic strategy resulted in reduced short-term glycaemic variability, although improvement in HbA1c was similar in both therapeutic groups.

In the AWARD-4 sub-study,[50] which was done over an initial period of 26 weeks and extended to 52 weeks, between-day glycaemic variability was slightly but significantly decreased with the once-weekly GLP-1 receptor agonist dulaglutide plus prandial insulin lispro, when compared with a basal-bolus insulin regimen of insulin glargine U100 plus prandial lispro. Improvements in ambient hyperglycaemia (percentage of participants within a glucose target range of 3·9–9·0 mmol/L), glycaemic variability, and risk of hypoglycaemia have been reported when a fixed-ratio combination of basal insulin degludec and the GLP-1 receptor agonist liraglutide was compared with either drug alone.[51]

Continuous subcutaneous insulin infusion in intensive:

Management

Use of CGM itself in self-management in T1DM has been found to have reduced MAGE by 10%, SD, hyperglycaemia time, hypoglycaemic time, and significant effect on QoL.[52]

DPP IV Inhibitor

Gliptins were endorsed as a monotherapy or add on therapy in drug naive type 2 diabetes. There was a significant decrease in glucose area under curve (AUC 0–2 h) after 2 year treatment with vildagliptin than in placebo group and also better effects in FBG and PPG as well as improvement in beta-cell function over 2-year treatment period.[53]

Modified Bariatric Surgery with Ileal Interposition

Metabolic surgery is a novel therapeutic approach done mainly in obese patients with poor glycaemic control in type 2 diabetes.[54] FBG, PPBG, and HbA1c have significantly improved. It was attributed to rapid stimulation of interposed ileal segment by ingested food leading to increased GLP-1 secretion.

CONCLUSION

Traditionally, diabetes management has focused on achieving normal plasma glucose levels. Recent studies suggest glycaemic variability may be an additional risk factor for the long-term complications of diabetes.

New diabetes management strategies should also

focus on minimising glycaemic variability.

Strategies to minimise glycaemic variability may include:

1. Intensive therapy with multiple insulin injections.
2. Use of rapid-acting insulin analogue to reduce periods of acute hyperglycaemia.
3. Use of long-acting insulin analogue to minimise basal or fasting blood glucose variability.
4. New insulin analogue may help achieve better glycaemic control and further reduce the risk for long-term complications

Diabetes management software can use the data from SMBG to give a measure of glycaemic variability. Use of SMBG, along with software allows the patient to monitor glycaemic excursions and identify any effect of behaviour or treatment schedule on glycaemic variability and control. Large-scale studies are needed to validate the impact of reducing glycaemic variability with these new treatment strategies, and monitoring systems.

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