Glycemic variability: Clinical implications

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ABSTRACT
Glycemic control and its benefits in preventing microvascular diabetic complications are convincingly proved by various prospective trials. Diabetes control and complications trial (DCCT) had reported variable glycated hemoglobin (HbA1C) as a cause of increased microvascular complications in conventional glycemic control group versus intensive one. However, in spite of several indirect evidences, its link with cardiovascular events or macrovascular complications is still not proved. Glycemic variability (GV) is one more tool to explain relation between hyperglycemia and increased cardiovascular risk in diabetic patients. In fact GV along with fasting blood sugar, postprandial blood sugar, HbA1C, and quality of life has been proposed to form glycemic pentad, which needs to be considered in diabetes management. Postprandial spikes in blood glucose as well as hypoglycemic events, both are blamed for increased cardiovascular events in Type 2 diabetics. GV includes both these events and hence minimizing GV can prevent future cardiovascular events. Modern diabetes management modalities including improved sulfonylureas, glucagon like peptide-1 (GLP-1)-based therapy, newer basal insulins, and modern insulin pumps address the issue of GV effectively. This article highlights mechanism, clinical implications, and measures to control GV in clinical practice.

Key words: Diabetes mellitus, glycemic variability, incretins, oxidative stress

INTRODUCTION
Glycemic variability (GV) means swings in blood glucose level. Diminished or absent glycemic auto regulation or short falls of insulin availability are hypothesized to be the etiological factors for these glycemic bumps. Intermittent high blood glucose exposure rather than constant high blood glucose exposure has been shown to have deleterious effect in experimental studies.[1-3] Physicians in their day to day practice, utilize quantitative values of glycemic parameters such as fasting, postprandial blood glucose, and glycated hemoglobin (HbA1C). In present era of targeting optimum glycemic control, it is also important to focus on GV as an additional goal point along with the traditionally followed parameters. Variations in HbA1C were proposed to contribute to development of microvascular complications like retinopathy and nephropathy in diabetes control and complications trial (DCCT) group.[4] In the event of new therapeutics in the management of type 2 diabetes mellitus by glucagon like peptide-1 (GLP-1) analogs and dihydropeptidyl peptidase-IV (DPP-IV) inhibitors through incretin mimetic effect, studying GV in an individual to achieve glycemic control is promising. The current article reviews the clinical perspectives of GV and understanding its role toward contribution of glycemic control in diabetic patients.

GLYCEMIC VARIABILITY—DEFINITION
The broad definition of GV takes into account the intraday glycemic excursions including episodes of hyper and hypoglycemia. The postprandial hyperglycemic excursions too contribute to GV. The occurrence of various microvascular and macrovascular complications in diabetes is attributed by various studies to hyperglycemia and dysglycemia (peaks and nadirs).[7-11] Several pathophysiological mechanisms were put forward,[12,13] unifying the two main mechanisms: Excessive protein glycation end products and activation of oxidative stress in the causation of vascular complication respectively.[14-17]
GV IS AS IMPORTANT AS HbA1C

The type 1 diabetes patients in DCCT intensively treated group had lesser microvascular complications than conventionally treated group. HbA1c variability was proposed to explain the development of retinopathy and nephropathy in conventional group.[6] 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 glycemic stability and its direct consequence, an excess rate of glycation.[18-20] However, there are other mechanisms in the development of diabetic complications and the fact that it is the exposure of glucose, which is measured by standard A1c, and does not include the peaks and nadirs.

The new formula devised by David M Nathan, takes into consideration of multiple self monitored blood glucose values and is depicted as ‘A1c Derived Average Glucose’ (ADAG): eAG (mg/dl) = 28.7 × A1C-46.7.[21,22] The average derived value which includes GV might explain in diabetic complication of hypoglycemia with near normal HbA1c in the DCCT group.

GV AND DAY TO DAY CONTROL

The Staub-Traugott effect,[23] improvement of carbohydrate tolerance following repeated glucose administration was proposed as early as 1921. This effect has been demonstrated after oral and intravenous administration of glucose. Sandra Bonuccelli et al. in their study using two sequential, equal oral glucose loads over a 6-h time period concluded that, higher glycemic excursions in response to the first load was associated with a higher potentiation factor during the second load, suggesting that the priming effect of hyperglycemia was the basis for the subsequent potentiation of insulin secretion. Glucose potentiation and stronger suppression of endogenous glucose release are the main mechanisms underlying the Staub-Traugott effect. Improved tolerance to sequential glucose loading is an important determinant of day-to-day glycemic exposure, suggesting how glycemic exposures are minimized in our body.

GV AS THERAPEUTIC END POINT

The target GV has been a topic of debate, it was proposed by Monnier et al.,[19] that 40 mg/dl as the target level of glucose variability and more so glucose variability was found to be independent predictor of chronic diabetic complications besides HbA1c. In nondiabetic critically ill patients diminishing hyperglycemic excursions will improve mortality. Also as in recent studies like action to control cardiovascular risk in diabetes (ACCORD) study, it is to be noted that hypoglycemia need to be avoided.

MEASUREMENT OF GV: METHODS AND THEIR LIMITATIONS [TABLE 1]

M-value
Developed by Schlichtkrull et al.[24] in 1964 using six self-monitored blood glucose (SMBG) per 24 h. The ideal glucose initially proposed was 120 mg/dl and in final formulae it was left to investigator, making it difficult to compare different studies that use different ideal glucose values. The M-value is zero, with GV it increases. The limitation lies in the fact that it does not take glycemic excursions in between readings.

Mean amplitude of glycemic excursions
It was described by Service et al.[25] using hourly obtained

Table 1: Formulae used to measured glycemic variability SD-Standard deviation, CV- Coefficient of variation, MAGE- Mean amplitude of glycemic excursions, CONGA- Continuous overall net glycemic action, MODD- Mean of daily differences, SMBG- Self monitored blood glucose, CGM- Continuous glucose monitoring

(Adapted from Siegelaar SE, et al.Endocrine Reviews. 2010;31:171-82)
blood glucose values over 48 h. Mean glucose value rather than the ideal glucose is referred to by summing absolute rises and falls encountered in a day. Continuous glucose monitoring uses Mean amplitude of glycemic excursions (MAGE).

**Continuous overlapping net glycemic action**
Proposed by McDonnell et al.\[26\] it is a continuous glucose monitoring (CGM)-based intraday GV. The Standard deviation (SD) of summated differences between a current observation and observation \(n\) hours previously gives the value.

**Absolute mean of daily differences**
The inter day GV measurement supplements MAGE and mean blood glucose (MBG). It was proposed by Molnar et al.\[27\] taking into mean absolute value differences of glucose of two consecutive days at the same time. It was developed using hourly blood sample during 48 h. It ignores excursions of less than 1 SD.

**Standard deviation**
It is the easiest method using seven point SMBG. However, it can miss certain peaks and nadirs occurring in between readings. The inter day variation can also be calculated by SD of fasting glucose concentrations\[28\] and is a measure of long-term glucose variability, but misses in all other intraday glucose values.

**Co-efficient of variation**
Using seven point blood glucose monitoring, calculated Co-efficient of variation (CV) corrects for the mean. CGM can be used to derive SD and CV, but in daily practice it becomes difficult.

Thus in search for glucose stability, the glycemic excursions were taken into consideration from middle of the 20th century putting forward various measuring parameters, mean glucose values in comparison to ideal glucose,\[24\] measuring glycemic excursions,\[25\] MAGE, Continuous overlapping net glycemic action (CONGA), Mean of daily differences (MODD), glucose levels computed to CGM, and liability index based on the change in glucose levels over time.\[29,30\] Risk of daily GV is not expressed by SD or CV. To overcome this, Kovatchev et al. suggested that low and high blood glucose indice (LBGI and HBGI) and average daily risk range (ADRR) parameters derived from SMBG\[31-33\] to address the risk of GV.

**Others**
Serum levels of 1,5-anhydroglucitol (1,5-AG) was suggested as marker of glycemic excursions. Its absorption is inhibited by excessive excretion of urinary glucose, the higher the plasma glucose concentration (above renal threshold), the lower the plasma 1,5-AG concentration. However, its use is limited in glucose fluctuations below renal glucose threshold.\[34\] Similarly correlation between 1,5-AG and HbA1c was weak above 8%. It is useful when evaluating postprandial hyperglycemic excursions HbA1c below 8%.

**MECHANISM OF GV INDUCED OXIDATIVE STRESS [FIGURE 1]**
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 formation of advanced glycation end products, activation of protein kinase C (PKC) and nuclear factor- \(\kappa\)B and increased hexosamine pathway flux. Through these pathways, increased intracellular reactive oxygen species (ROS) cause defective angiogenesis in response to ischemia, activate a number of proinflammatory pathways, and cause long-lasting epigenetic changes that drive persistent expression of proinflammatory genes after glycermia is normalized (‘hyperglycemic memory’).\[35\] In a study by Quagliaro et al. involving human umbilical vein endothelial cells exposure to intermittent high glucose versus exposure to stable high glucose environment, there was apoptosis of endothelial cells exposed to intermittent high glucose. This may be related to ROS overproduction, through PKC-dependent activation of nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase.

Contributions of fasting plasma glucose and postprandial glucose to oxidative stress were shown in several studies.\[35-38\] Monnier et al., in his study showed that in type 2 diabetes
patients acute glucose fluctuations were strongly correlated with the triggering of oxidative stress and there was no relationship between urinary levels of 8-iso-PGF2α (marker of oxidative stress) and markers of chronic hyperglycemia.\[19\]

In type 2 diabetes patients, hyperglycemic clamp study was done, compared with healthy subjects in a case control study by Ceriello et al. Different concentration of glucose were given as single spike or oscillating between basal and high levels over a 24-h period. Twenty four hour after the clamp, endothelial function was measured using flow-mediated dilation of the brachial artery. 3-nitrotyrosirone and 24-h urinary levels of 8-iso PGF2α were measured as markers of oxidative stress. Impaired endothelial function was observed with higher levels of oxidative stress in oscillating glucose than stable constant high glucose.\[39\]

There is a strong scientific evidence to suggest that oxidative stress is related to glycemic excursions\[1-5,39\], however, the interventional studies have not been able to consistently demonstrate the relationship and moreover antioxidant therapy did not reduce the vascular complication.\[39-41\] Recently identification of window period for oxidative stress intervention was observed to explain the controversial results of human clinical trials by Zuolin Zhu et al.\[42\]

**GV and Hypoglycemia**

In DCCT trial 10-30% incidence of hypoglycemia was observed in intensive insulin arm group. Hypoglycemia was the main accompanying complication when desired glucose target is intensively achieved. The frequency of severe hypoglycemia increases exponentially when lowering blood glucose\[43\] and several studies have reported that low glucose variability coincided with decreased occurrence of hypoglycemia.\[44\] Glucose variability was mentioned as measure of predictor of future severe hypoglycemia than HbA1c by Cox et al.\[45\] In a study by Kilpatrick et al., using datasets of the DCCT found that glucose variability, calculated as SD of SMB and MAGE was independently predictive of hypoglycemia just like MBG and other study. Diabetes outcomes in veterans study (DOVES) also found the association of risk of hypoglycemia as much related to glucose variability as to the mean glucose value.\[46,47\] Limiting glycemic excursions at the same time maintaining the MBG and HbA1c in target range can be a tool in achieving glycemic control.

**GV and Diabetic Microvascular Complications**

Bragd et al. found that GV was an independent predictor of the prevalence of peripheral neuropathy, however, no significant relationship was found between GV and the development of other microvascular complications such as retinopathy or nephropathy in the cohort.\[49\] Additionally, GV was borderline predictor of incidence of peripheral neuropathy, suggesting that nervous system may be vulnerable to GV. But Kilpatrick et al. using data from DCCT, assessed glucose variability around MBG. They found out that MBG was significantly associated with the development of diabetic retinopathy but not with that of nephropathy. There was no relation between the measures of GV and the development or progression of either retinopathy or nephropathy.\[49\]

In T2DM patients, CV of FBG, a measure of GV was found to have association of diabetic retinopathy progression to higher CV-fasting blood glucose (FBG) values, in a 5 year follow-up prospective cohort study by Gimeno-Orma et al. In addition the incidence of diabetic retinopathy increased with increased FBG variability quartiles.\[48\]

In another study in elderly patients (Verona Diabetes Study), it is the magnitude of hyperglycemia, measured by M-FBG and HbA1c, strongly predicted the development and progression of diabetic retinopathy in elderly patients with type 2 diabetes. The glucose variability measured by CV-FBG was not associated with retinopathy progression. However, in cross sectional analysis, CV-FBG was significantly associated with the presence of diabetic retinopathy.\[51\]

Painful neuropathy was found to be related increased glucose flux. Oyibo et al.\[52\] in their study found patients with painful neuropathy had greater MBG, M-value than patients without pain. However, no significant difference was found in the MAGE value. GV seemed to have an effect on autonomic neuropathy, but this effect disappeared when the model was adjusted for HbA1c or AUC. There are few ongoing trials studying effect of GV on autonomic tone in hospitalized patients with Type 2 diabetes.\[53\]

**GV and Cardiovascular Health**

The analysis of DCCT data by Kilpatrick et al. showed that pre- and postprandial blood glucose, MBG were significantly related to cardiovascular disease (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 glycemic control including MBG, HbA1c, and within-day SDBG.\[54\]

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
Diet-induced weight loss can significantly improve not only insulin sensitivity but also β-cell function, capable of reducing glucose levels and delaying the progression from impaired glucose tolerance (IGT) to diabetes.\[65,66\] Recently a research study on diet of high glycemic meal with pistachio nuts has shown blunted postprandial response. The study assessed glucose and insulin responses over 3 h, as well as glucose-dependent insulinotropic peptide and glucagon-like-peptide-1 and gherlin.

**Drugs and GV**

**Oral hypoglycemic agents**

Using continuous interstitial glucose sensor monitoring system (CGMS) measures of glucose intraday variability, MAGE, SD, mean glucose levels, CONGA and interday variability, MODD were found 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 between the two.\[63\] It was observed that medications such as acarbose that target postprandial hyperglycemia not only attenuate glycemic excursions but also reduce oxidative stress and potentially improve endothelial dysfunction.\[64,65\] Bao et al.\[70\] showed that controlled-release glipizide combined with acarbose was more effective in reducing MAGE than controlled-release glipizide monotherapy.

Glimepiride logically should cause less GV 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 the possible mechanisms.\[71,72\] The insulin-releasing activity is high with glibenclamide and lowest with glimeperide.\[72\]

**Prandial insulins**

There is attenuation and progressive delay of prandial insulin response contributing to increasing hyperglycemia in established T2DM. An important consequence of this derangement is that hepatic glucose production is no longer suppressed during times of prandial glucose intake leading to hyperglycemic excursions. Over and above due to longer duration of action, inter meal hypoglycemia is quite common with regular insulin. Newer rapid prandial insulin analogs are rapidly absorbed and their action closely mimics the normal physiological insulin response to meals. Prandial dosage allows to be adjusted on the premeal blood glucose concentration and the estimated carbohydrate content of the meal, using a predetermined correction factor for treating elevated glucose levels and an insulin-carbohydrate ratio to match the insulin dose to the carbohydrate load.

**Basal insulins**

In ‘The Treat-to-Target Trial’ addition of long acting basal insulin glargine at bed time in comparison to

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**GV and Quality of Life**

Frequent fluctuations in blood glucose with hypoglycemia and glycemic excursions affect individuals’ mood changes with more diabetic complications, depression and poor quality of life. Large GV was found to be associated with low quality of life than HbA1c and 24 h average blood glucose.\[60\] In achieving glycemic target, patient reported outcomes (PROs) in addition to the physician’s reported outcomes by way of measuring HbA1c, FBG is considered in overall management of diabetes. PROs include various measures, including quality of life (QoL), as well as indices related to treatment satisfaction, mental health, social life, and diabetes management and well being. The tools include like MIND youth questionnaire, Diab Met Sat Questionnaire.\[61-63\] The Diab Met Sat questionnaire has 21 items which can be assessed a an overall score or as three subscales: Burden (11 items), symptoms (5 items) and efficacy (5 items), and efficacy (5 items). In fact, the diabetic subjects are bogged down with various neuropsychiatric illnesses, which need to be screened for optimum patient management.\[63\] QoL along with GV, FBG, PPG, and HbA1c form the pillars of glycemic pentad, which needs to be viewed in effective diabetes management.\[64\]

**Measures to minimize GV**

**Life style measures**

Diet-induced weight loss can significantly improve not only insulin sensitivity but also β-cell function, capable of

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neutral protamine hagedorn (NPH) insulin in a poorly controlled on oral agents in overweight randomized type 2 diabetic patients seeking a target fetal bovine serum (FBS) ≤100 mg/dl, had better glycemic control with lesser episodes of hypoglycemia.\(^{[73]}\) It was attributed to better GV in the glargine group. The 8-point self-monitored glucose profile showed less within subject variability of FBG.

In an another study LANMET\(^{[74]}\) 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 glucose fluctuations from peaks to nadirs, whatever the type of insulin used.

**Basal bolus insulin therapy**

An alternative to basal bolus insulin therapy to provide constant 24 h base line insulin and covering meal time glycemic excursions as mentioned above, near mimicking to endogenous insulin availability with premixed 50/50 mealtime plus metformin in type 2 diabetes patients who were on 0–2 insulin injections per day were studied by Robbins et al.\(^{[75]}\) The overall HbA1c levels and preprandial blood glucose and PPBG were lower (except FBG) with similar reduction in nocturnal hypoglycemia and less GV, compared with Glargine and Metformin.

**Continuous subcutaneous insulin infusion in intensive management**

With more use of CGM system GV was more evident in patients with similar HbA1c levels. (CSII) Continuous Subcutaneous Insulin Infusion was considered as alternative when glycemic control was not achieved with use of multiple dose insulin regimen in Type 1 diabetic patients.\(^{[76]}\) Use of CGM itself in self management in T1DM has been found to have reduced MAGE by 10%, SD, hyperglycemic time, hypoglycemic time, and significant effect on QoL.\(^{[77]}\) Chimenti et al. observed that improvement of glycemic control after CSII was associated with reduction in SD, mean glucose, duration, and magnitude of hyperglycemic excursions with no changes in the fasting night period or in duration or magnitude of the hypoglycemic excursions.\(^{[78]}\)

**GLP-1 analogues**

Glucose-dependent insulinoceptive peptide (GIP) and GLP-1 activation of incretin receptors on β-cells increases insulin release in response to glucose and has additional benefits of enhanced glucose disposal in peripheral tissues and protection against ischemia/reperfusion injury.\(^{[79,80]}\) In critical care setting, glucose variability is a predictor of mortality and was set as important goals in glucose management in intensive care unit (ICU). MAGE a measurement of GV was found to be lower in patients receiving exenatide in severely burned pediatric patients\(^{[81]}\) and resulted in a reduced amount of exogenous insulin. In another study, Exenatide in comparison with insulin glargine had better postprandial glucose profile and significant reduction in ADRR, a sensitive predictor of either hyper-hypoglycemia despite similar reductions in A1C.\(^{[73]}\) Exenatide had better effect on reducing GV when compared with glimepiride treatment. The benefits imparted by exenatide could be explained by glucose dependent stimulation of insulin secretion and concomitant suppression of glucagons.\(^{[82]}\)

**DPP-1 V inhibitors**

Vildagliptin, Sitagliptin, Saxagliptin, and other DPP-IV inhibitors increase endogenous GIP and GLP-1 by inhibiting their degradation. Glitipins were endorsed as a monotherapy or add on therapy in drug naïve 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 postprandial glucose as well as improvement in β-cell function over 2 year treatment period.\(^{[83]}\) The study examined influence of 2-year treatment with vildagliptin (50 mg once daily) on glycemic control and B-cell function in patients with T2DM and mild hyperglycemia. In the same study observation of decreased hyperglycemia period during 1 year treatment period and increase in 4 week wash out period explains that glycemic control is closely regulated with glycemia state and β-cell responsiveness. Sitagliptin significantly reduced blood 2 and 24 h AUC, MBG, and reduction in time spent in euglycemic range in adult patients with T1DM.\(^{[84]}\)

**Modified bariatric surgery with ileal interposition**

Metabolic surgery is a novel procedure done mainly in obese patients with poor glycemic control in T2DM.\(^{[85-88]}\) We have previously demonstrated that even nonobese subjects with poorly controlled diabetes on oral hypoglycemic agents (OHA)/insulin were found to have better glycemic control without any requirement of exogenous insulin after ileal interposition with sleeve gastrectomy/diverted sleeve gastrectomy.\(^{[89-92]}\) FBG, PPBG, and HbA1c have significantly improved. It was attributed to rapid stimulation of interposed ileal segment by ingested food leading to augmented GLP-1 secretion.

**CONCLUSION**

Over and above standard glycemic parameters like blood glucose and glycated hemoglobin, GV can be a future target parameter for optimum glycemic control. This could be applicable to all T1DM, T2DM, gestational diabetes, and probably nondiabetic critically ill patients. Studies have
shown improved outcomes for micro and to some extent macrovascular diabetic complications by minimizing GV. 
In spite of various formulas offered, simple and standard clinical tool to define GV is yet to evolve. Current diabetes medicines like incretin mimetics, newer basal and prandial insulins, CSII and modern bariatric surgical techniques in obese type 2 diabetic patients significantly reduce GV.

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