Review Article

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.[1-5] 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.[6] 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.

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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]

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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 carbohydrated 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

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 $M_{GR}=\frac{\sum_{t=t_i}^{t_n}\lvert 10\log\frac{GR_t}{IGV}\rvert^3}{n}$ and $M_W=\frac{G_{max}-G_{min}}{20}$	M_{GR} = M-value for glucose readings M_W = correction factor for n <24 GR_t = 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	$\sqrt{\frac{\sum_{t=t_1}^{t_n}(D_t-\bar{D})^2}{k^*-1}}$ where $D_t=GR_t-GR_{t-m}$ and $\bar{D}=\frac{\sum_{t=t_1}^{t_n}D_t}{k^*}$	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	$\frac{\sum_{t=t_1}^{t_n}\lvert GR_t-GR_{t-1440}\rvert}{k^*}$		inter-day variation

(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 summating 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- κB 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 glycemia 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

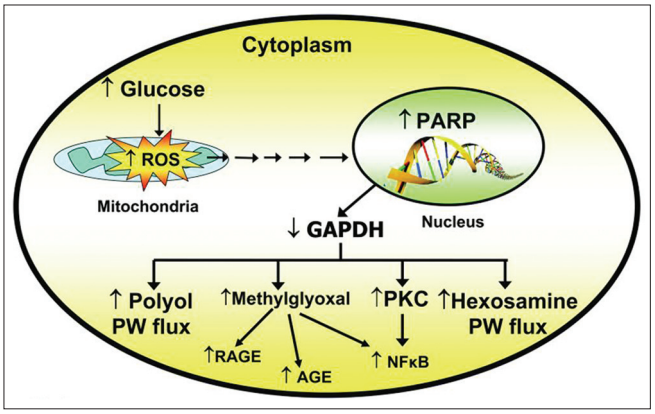

Figure 1: Pathophysiological mechanism of hyperglycemia induced cellular damage mediated by oxidative stress. ROS- Reactive oxygen species, PARP- Poly adenosyl ribose phosphate, GAPDH- Glyceraldehyde 3-phosphate dehydrogenase, PKC-Protein kinase C, NF and #954; B-Nuclear factor kappa B, AGE-Advanced glycation end products, RAGE-Receptor for advanced glycation end products, PW-Pathway (Adapted from Giacco F *et al.*, Circ Res. 2010; 107: 1058-70)

patients acute glucose fluctuations were strongly correlated with the triggering of oxidative stress and there was no relationship between urinary levels of 8-iso-PGF 2α (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.[48] 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.[50]

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.[52]

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, GV was positively associated with changes in systolic and diastolic blood pressure.[54,55]

In elderly Type 2 diabetes patients, Verona Diabetes Study, the authors concluded that CV-FPG is an independent predictor of all cause-mortality, with mortality increasing with increasing CV-FPG. These results suggest glucose variability has a greater effect on survival in elderly patients with type 2 DM more than the degree of metabolic control, the severity of hyperglycemia or the progression toward lower or higher FPG levels over time.[56] In an extension of Verona Diabetes Study, patients with T2DM aged 56-74 years, CV-FPG was found to be an independent predictor of both CVD and malignancy-related mortality.[57]

In multivariate analyses, glucose peak was a significant independent determinant of carotid intima-media thickness (CIMT) and explained 49% of the variability.[58] In a recent study of type 2 diabetes mellitus with stroke, post prandial blood glucose (PPBG) was significantly associated with CIMT and stroke.[59]

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 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 glucagons-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.[67] 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.[68,69] 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

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 end point, 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.[76] 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.[77,78]

GLP-1 analogues

Glucose-dependent insulinotropic 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.[33] Exenatide had better effect on reducing GV when compared with glimerpiride 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. 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 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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References

1. Quagliaro L, Piconi L, Assaloni R, Martinelli, Motz E, Ceriello A. Intermittent high glucose enhances apoptosis related to oxidative stress in human umblical vein endothelial cells: The role of protein kinase C and NAD(P) H-oxidase activation. Diabetes 2003;52:2795-804.
2. Piconi L, Quagliaro L, Assaloni R, Da Ros R, Maier A, Zuodar G, *et al*. Constant and intermittent high glucose enhances endothelial cell apoptosis through mitochondrial superoxide overproduction. Diabetes Metab Res Rev 2006;22:198-203.
3. Takeuchi A, Throckmorton DC, Brogen AP, Yoshizawa N, Rasmussen H, Kashgarian M. Periodic high extra cellular glucose enhances production of collagens III and IV by mesangial cells. Am J Physiol 1995;268 (1 Pt 2):F13-9.
4. Jones SC, Saunders HJ, Qi W, Pollock CA.Intermittent high glucose enhances cell growth and collagen synthesis in cultured human tubulointerstitial cells. Diabetologia 1999;42:1113-9.
5. Hovath EM, Benko R, Kiss L, Muranyi M, Pek T, Fekete K, *et al*. Rapid glycaemic swings induce oxidative stress, activate poly-(ADP-ribose) polymerase and impair endothelial function in a rat model of diabetes mellitus. Diabetologia 2009;52:952-61.
6. Kilpatrick ES, Rigby AS, Atkin SL. A1c Variability and the risk of microvascular complications in type 1 diabetes: Data from the DCCT, Diabetes Care 2008;31:2198-202.
7. Stratton IM, Adler AI, Neil HA, Mathews DR, Manley SE, Cull CA, *et al*. Association of glycaemia with macrovascular and microvascular complications of type 2 diabets (UKPDS 35): Prospective observational study. BMJ 2000;321:405-12.
8. Raz I, Wilson PW, Strojek K, Kowalska I, Bozikov V, Gitt AK, *et al*. Effects of prandial versus fasting glycemia on cardiovascular outcomes in type 2 diabetes: The HEART 2D trial. Diabetes Care 2009;32:381-6.
9. Kota SK, Kota SK, Jammula S, Panda S, Modi KD. Effect of diabetes on alteration of metabolism in cardiac myocytes: therapeutic implications. Diabetes Technol Ther 2011;13:1155-60.
10. Kota SK, Meher LK, Jammula S, Kota SK, Krishna SV, Modi KD. Aberrant angiogenesis: The gateway to diabetic complications. Indian J Endocrinol Metab 2012;16:918-30.
11. Hari Kumar KV, Kota SK, Basile A, Modi KD. Profile of microvascular disease in type 2 diabetes in a tertiary health care hospital in India. Ann Med Health Sci Res 2012;2:103-8.
12. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. Nature 2001;414:813-20.
13. Brownlee M. Banting lecture 2004. The pathobiology of diabetic complications: A unifying mechanism. Diabetes 2005;54:1615-25.
14. Avignon A, RAdauceanu A, Monnier L. Nonfastingplasma glucose is a better marker of diabetic control than fasting plasma glucose in type 2 diabetes. Diabetes Care 1997;20:1822-36.
15. Bonora E, Calcaterrrs F, Lombardi S, Bonfante N, Formentini G, Bonadonna RC, *et al*. Plasma glucose levels throughout the day and HbA1c interrelationships in type 2 diabetes: Implications for treatment and monitoring of metabolic control. Diabetes Care 2001;24:2023-9.
16. El-Kebbi IM, Ziemer DC, Cook CB, Gallina DL, Barnes CS, Phillipps LS. Utility of casual postprandial glucose levels in type 2 diabets management. Diabetes Care 2004;27:335-9.
17. Nathan DM, Kuenen J, Borg R, Zheng H, Schoenfeld D, Heine RJ; A1c-Derived average glucose study group. Translating the A1c assay into estimated average glucose values. Diabetes Care 2008;31:1473-8.
18. Abhyuday V, Muthukrishnan J, Harikumar KVS, Modi KD. HbA1c and average blood glucose. Calicut Medical Journal 2009;7:e3.
19. Monnier L, Colette C. Glycemic variability. Should we and can we prevent it? Diabetes Care 2008;31 Suppl 2:S150-4.
20. Ceriello A, Ihnat MA. Glycemic Variability. A new therapeutic challenge in diabetes and the critical care setting. Diabet Med 2010;27:862-67.
21. Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, *et al*. Intensive insulin therapy in critically ill patients. N Engl J Med 2001;345:1359-67.
22. Miller ME, Byington RP, Goff DC Jr, Bigger JT, Buse JB, Cushman WC, *et al*. The action to control cardiovascular risk in diabetes study group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545-59.
23. Bonuccelli S, Muscelli E, Gastaldelli A, Barsotti E, Astiarraga BD, Holst JJ *et al*. Improved tolerance to sequential glucose loading (Staub-Traugott effect): Size and mechanisms. Am J Physiol Endocrinol Metab 2009;297:E532-7.
24. Schlichtkrull J, Munck O, Jersild M. The M-value, an index of blood sugar control in diabetes. Acta Med Scand 1965;177:95-102.
25. Service FJ, Molnar GD, Rosevear JW, Ackerman E, Gatewood LC, Taylor WF. Mean amplitude of glycemic excursions, a measure of diabetic instability. Diabetes 1970;19:644-55.
26. Mc Donnell CM, Donath SM, Vidamar SI, Werther GA, Cameron FJ. A novel approach to continuous glucose analysis utilizing glycemic variation. Diabetes Technol Ther 2005;7:253-63.
27. Molnar GD, Taylor WF, Ho MM. Day-to-day variation of continuously monitored glycaemia: A further measure of diabetic instability. Diabetologia 1972;8:342-8.
28. Shima K, Tanaka R, Morishita S, Tarui S, Kumahara Y. Studies on the etiology of "brittle diabetes". Relationship between diabetic instability and insulinogenic reserve. Diabetes. 1977;26:717-25.
29. Kovatchev BP, Cox DJ, Gonder-Frederick LA, Clarke W. Symmetrization of the blood glucose measurement scale and its applications. Diabetes Care 1997;20:1655-8.
30. Ryan EA, Shandro T, Green K, Paty BW, Senior PA, Bigam D, *et al*. Assessment of the severity of hypoglycemic and glycemic lability in type 1 diabetic subjects undergoing islet transplantation. Diabetes 2004;53:955-62.
31. Kovatchev BP, Otto E, Cox D, Gonder-Frederick L, Clarke W. Evaluation of a new measure of blood glucose variability in diabetes. Diabetes Care 2006;29:2433-38.
32. Kovatchev BP, Clarke WL, Breton M, Brayaman K, McCall A. Quantifying temporal glucose variability in diabetes via continuous glucose monitoring: Mathematical methods and clinical application. Diabetes Technol Ther 2005;7:849-62.
33. McCall AL, Cox DJ, Brodows R, Crean J, Johns D, Kovatchev B. Reduced daily risk of glycemic variability: Comparison of exenatide with insulin glargine. Diabetes Technol Ther 2009;11:339-44.
34. Buse JB, Freeman JL, Edelman SV, Jovanovic L, McGill JB. Serum

1,5-anhydroglucitol (GlycoMark): A short-term glycemic marker. Diabetes Technol Ther 2003;5:355-63.
35. Giacco F, Brownlee M. Oxidative stress and diabetic complications. Circ Res 2010;107:1058-70.
36. Monnier L, Mas E, Ginet C, Michel F, Villon L, Cristol JP, *et al*. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. JAMA 2006;295:1681-7.
37. Ceriello A. Postprandial hyperglycemia and diabetes complications: Is it time to treat? Diabetes 2005;54:1-7.
38. Natarajan R, Lanting L, Gonzales N, Nadler J. Formation of an F2-isoprostane in vascular smooth muscle cells by elevated glucose and growth factors. Am J Physiol 1996;271 (1 Pt 2):H159-65.
39. Ceriello A, Esposito K, Piconi L, Ihnat MA, Thorpe JE, Testa R, *et al*. Oscillating glucose is more deleterious to endothelial function and oxidative stress than mean glucose in normal and type 2 diabetic patients. Diabetes 2008;57:1349-54.
40. Jay D, Hitomi H, Griendling KK. Oxidative stress and diabetic cardiovascular complications. Free Radic Biol Med 2006;40:183-92.
41. Halliwell B, Gutteridge JM Free Radicals in Biology and Medicine. 4thed. New York: Oxford Univeristy Press; 2007.
42. Zhu Z. Identification of the window period for oxidative stress intervention. Journal of Diabetes and Endocrinology 2011:2;20-3.
43. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977-86.
44. Jeha GS, Karaviti LP, Anderson B, Smith EO, Donaldson S, McGirk TS, *et al*. Insulin pump therapy in preschool children with type 1 diabetes mellitus improves glycemic control and decreases glucose excursions and the risk of hypoglycemia. Diabetes Technol Ther 2005;7:876-84.
45. Cox DJ, Kovatchev BP, Julian DM, Gonder-Frederick LA, Polonsky WH, Schlundt DG, *et al*. Frequency of severe hypoglycemia in insulin-dependent diabetes mellitus can be predicted from self-monitoring blood glucose data. J Clin Endocrinol Metab 1994;79:1659-62.
46. Murata GH, Hoffman RM, Shah JH, Wendel CS, Duckworth WC. A probabilistic model for predicting hypoglycemia in type 2 diabetes mellitus: The diabetes outcomes in veterans study (DOVES). Arch Intern Med 2004;164:1445-50.
47. Kilpatrick ES, Rigby AS, Goode K, Atkin SL. Relating mean blood glucose and glucose variability to the risk of multiple episodes of hypoglycaemia in type 1 diabetes. Diabetologia 2007;50:2553-61.
48. Bragd J, Adamson U, Bäcklund LB, Lins PE, Moberg E, Oskarsson P. Can glycaemic variability, as calculated from blood glucose self-monitoring, predict the development of complications in type 1 diabetes over a decade?. Diabetes Metab 2008;34:612-6.
49. Kilpatrick ES, Rigby AS, Atkin SL. The effect of glucose variability on the risk of microvascular complications in type 1 diabetes. Diabetes Care 2006;29:1486-90.
50. Gimeno-Orna JA, Castro-Alonso FJ, Boned-Juliani B, Lou-Arnal LM. Fasting plasma glucose variability as a risk factor of retinopathy in Type 2 diabetic patients. J Diabetes Complications 2003;17:78-81.
51. Zoppini G, Verlato G, Targher G, Casati S, Gusson E, Biasi V, *et al*. Is fasting glucose variability a risk factor for retinopathy in people with type 2 diabetes? Nutr Metab Cardiovasc Dis 2009;19:334-9.
52. Oyibo SO, Prasad YD, Jackson NJ, Jude EB, Boulton AJ. The relationship between blood glucose excursions and painful diabetic peripheral neuropathy: A pilot study. Diabet Med 2002;19:870-3.
53. Effect of glycemic variability on autonomic tone in hospitalized patients with type 2 diabetes. Available at http://clinicaltrials.gov/ct2/show/NCT01409239.
54. Kilpatrick ES, Rigby AS, Atkin SL. Mean blood glucose compared with HbA1c in the prediction of cardiovascular disease in patients with type 1 diabetes. Diabetologia 2008;51:365-71.
55. Gordin D, Rönnback M, Forsblom C, Mäkinen V, Saraheimo M, Groop PH. Glucose variability, blood pressure and arterial stiffness in type 1 diabetes. Diabetes Res Clin Pract 2008;80:e4-7.
56. Muggeo M, Verlato G, Bonora E, Zoppini G, Corbellini M, de Marco R. Long-term instability of fasting plasma glucose, a novel predictor of cardiovascular mortality in elderly patients with non-insulin-dependent diabetes mellitus: The Verona Diabetes Study. Circulation 1997;96:1750-4.
57. Muggeo M, Zoppini G, Bonora E, Brun E, Bonadonna RC, Moghetti P, *et al*. Fasting plasma glucose variability predicts 10-year survival of type 2 diabetic patients: The Verona Diabetes Study. Diabetes Care 2000;23:45-50.
58. Esposito K, Giugliano D, Nappo F, Marfella R; Campanian Postprandial Hyperglycemia Study Group. Regression of carotid atherosclerosis by control of postprandial hyperglycemia in type 2 diabetes mellitus. Circulation 2004;110:214-9.
59. Kota SK, Mahapatra GB, Kota SK, Naveed S, Tripathy PR, Jammula S, *et al*. Carotid intima media thickness in type-2 diabetes Mellitus with ischemic stroke. Indian J Endocrinol Metab (In press).
60. Penckofer S, Quinn L, Byrn M, Ferrans C, Miller M, Strang. Does glycemic variability impact mood and quality of life? Diabetes Technol Ther 2012;14:303-10.
61. de Wit M, Snoek FJ. The DAWN MIND youth program. Pediatr Diabetes 2009:13;46-9.
62. Brod M, Skovlund SE, Wittrup-Jensen KU. Measuring the impact of diabetes through patient report of treatment satisfaction, productivity and symptom experience. Qual Life Res 2006;15:481-91.
63. Kota SK, Meher LK, Jammula S, Krishna SV, Kota SK, Modi KD. Neuropsychiatric Screening in type 2 diabetes mellitus. Indian J Endocrinol Metab. 2012;16: S37-S40.
64. Kalra S, Kalra B. The glycemic pentad: Role of insulin analogues. Webmed Central Endocrinology 2010;1:WMC00562.
65. Kendall CW, Josse AR, Esfahani A, JenkinsDJ. The impact of pistachio intake alone or in combination with high-carbohydrate foods on post-prandial glycemia. Eur J Clin Nutr 2011;65:696-702.
66. Utzschneider KM, Carr DB, Barsness SM, Kahn SE, Schwartz RS. Diet-Induced weight loss is associated with an improvement in B-cell function in older men. J Clin Endocrinol Metab 2004;89:2704-10.
67. Lin SD, Wang JS, Hsu SR, Sheu WH, Tu ST, Lee IT, *et al*. The beneficial effect of alpha-glucosidase inhibitor on glucose variability compared with sulfonylurea in Taiwanese type 2 diabetic patients inadequately controlled with metformin: Preliminary data. J Diabetes Complications 2011;25:332-8.
68. Li Y, Xu L, Shen J, Ran J, Zhang Y, Wang M, *et al*. Effects of short-term therapy with different insulin secretagogues on glucose metabolism, lipid parameters and oxidative stress in newly diagnosed type 2 diabetes mellitus. Diabetes Res Clin Pract 2010;88:42-7.
69. Shimabukuro M, Higa N, Chnen I, Yanakawa K, Takasu N. Effects of a single administration of acarbose on postprandial glucose excursion and endothelial dysfunction in type 2 diabetic patients. A randomized cross over study. J Clin Endocrinol Metab 2006:91;837-42.
70. Bao YQ, Zhou J, Zhou M, Cheng YJ, Lu W, Pand XP, *et al*. Glipizide controlled-release tablets, with or without acarbose, improve glucose variability in newly diagnosed type 2 diabetes. Clin Exp Pharmacol Physiol 2010;37:564-8.
71. Davis SN. The role of glimepiride in the effective management of Type 2 diabetes. J Diabetes Complications 2004:18;367-76.
72. Muller G, Satho Y, Geisen K. Extrapancreatic effects of sulfonylureas-a comparison between glimepiride and conventional sulfonylureas. Diabetes Res Clin Pract 1995;28:S115-37.
73. Riddle MC, Rosenstoc J, Gerich J; Insulin Glargine 4002 Study Investigators. The Treat-to-target trial: Randomised addition of

glargine or human NPH insulin to oral therapy of type 2 diabetic patients. Diabetes Care 2003;26:3080-6.
74. Yki-Jarvinen H, Kauppinen-Makelin R, Tilikkainen M, Vahatalo M, Virtamo H, Nikkila K, *et al*. Insuling glargine or NPH combined with metformin in type 2 diabetes: The LANMET study. Diabetologia 2006;49:442-51.
75. Robbins DC, Beisswenger PJ, Ceriello A, Goldberg RB, Moses RG, Pagkalos EM, *et al*. Meal time 50/50 basal+prandial insulin analogue mixture with a basal insulin analogue, both plus metformin, in the achievement of target HbA1c and pre- and postprandial blood glucose levels in patients with type 2 diabetes; a multinational, 24-week, randomized, open-lable, parallel-group comparison. Clin Ther 2007:29;2349-64.
76. Pickup J, Keen H. Continuous subcutaneous insulin infusion at 25 years: Evidence base for the expanding use of insulin pump therapy in type 1 diabetes. Diabetes Care 2002;25:593-8.
77. Chimenti EM, de la Morena LH, Vaquero PM, Saez-de-Ibarra L, Domínguez MG, Sánchez LF. Assessing glycaemic variability with continuous glucose monitoring system before and after continuous subcutaneous insulin infusion in people with type 1 diabetes. Diabetes Res Clin Pract 2010;90:e57-9.
78. Danne T, de Valk HW, Kracht T, Walte K, Geldmacher R, Sölter L, *et al*. Reducing glycemic variability in type 1 diabetes self-management with a continuous glucose monitoring system based on wired enzyme technology. Diabetologia. 2009;52:1496-503.
79. Drucker DJ, Chapman MJ, Mojsov S, Chick WL, Habener JF. Glucagon-like peptide 1 stimulates insulin gene expression and increases cyclic AMP in levels in a rat islet cell line. Proc Natl Acad Sci U S A 1987;84:3434-8.
80. Pratley RE, Gilbert M. Targetting Incretins in Type 2 Diabetes: Role of GLP-1 receptor agonists and DPP-4 inhibitors. Rev Diabet Stud 2008;5:73-94.
81. Mecott GA, Herndon DN, Kulp GA, Brooks NC, Al-Mousawi AM, Kraft R, *et al*. The use of exenatide in severely burned pediatric patients. Crit Care 2010:14;R153.
82. Irace C, Fiorentino R, Carallo C, Scavelli F, Gnasso A. Exenatide improves glycemic variability assessed by continuous glucose monitoring in subjects with type 2 diabetes. Diabetes Technol Ther 2011;13:1261-3.
83. Scherbaum WA, Schweizer A, Mari A, Nilsson PM, Lalanne G, Wang Y, *et al*. Evidence that vildagliptin attenuates deterioration of glycaemic control during 2-year treatment of patients with type 2 diabetes and mild hyperglycemia. Diabetes Obes Metab 2008;10:1114-24.
84. Ellis SL, Moser EG, Snell-Bergeon JK, Rodionova AS, Hazenfield RM, Garg SK. Effect of sitagliptin on glucose control in adult patients with type 1 diabetes: A pilot, double-blind, randomized, cross over trial. Diabet Med 2011;28:1176-81.
85. Hari Kumar KV, Ugale S, Gupta N, Naik V, Kumar P, Bhaskar P, *et al*. Ileal transposition with sleeve gastrectomy for control of type 2 diabetes. Diabetes Technol Ther 2009;11:1-5.
86. Depaula AL, Macedo AL, Rassi N, Machado CA, Scharibman V, Silva LQ, *et al*. Laparoscopic treatment of type 2 diabetes mellitus for patients with a body mass index less than 35. Surg Endosc 2008;22:706-16.
87. Tinoco A, El-kadre L, Aquiar L, Tinoco R, Savassi-Rocha P. Short-term and mid-term control of type 2 diabetes mellitus by laparoscopic sleeve gastrectomy with ileal interposition. World J Surg 2011;35:2238-44.
88. Strider AD, Vahl PV, Jandacek RJ, Woods SC, D'Alessio DA, Seely RJ. Weight loss through ileal transposition is accompanied by increased ileal hormone secretion and synthesis in rats. Am J Physiol Endocrinol Metab 2005;288:E447-53.
89. Kumar Kota S, Ugale S, Gupta N, Naik V, Krishna Kota S, Hari Kumar KV, *et al*. Remission of Type 2 Diabetes Mellitus by Ileal Interposition with Sleeve gastrectomy. Int J Endocrinol Metab 2011;9:374-81.
90. Kota SK, Ugale S, Gupta N, Naik V, HarikumarKVS, Modi KD. Ileal Interposition with sleeve gastrectomy for treatment of type 2 diabetes. Indian J Endocrinol Metab 2012;16:589-98.
91. Kota SK, Ugale S, Gupta N, Modi KD. Laparoscopic ileal interposition with diverted sleeve gastrectomy for treatment of type 2 diabetes. Diabetes Metab Syndr 2012;6:125-31.
92. Kota SK, Ugale S, Gupta N, Krishna SV, Modi KD. Ileal Interposition with Diverted sleeve gastrectomy for treatment of Type 2 diabetes. Indian J Endocrinol Metab 2012;16 Suppl 2:S458-9.

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