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CLINICAL PERSPECTIVES OF GLYCEMIC VARIABILITY AND UNDERSTANDING ITS ROLE TOWARDS CONTRIBUTION OF GLYCEMIC CONTROL IN DIABETIC PATIENTS

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ABSTRACT

Diabetes mellitus word is came from the Greek phrase diabetes, that means siphon - to pass through and the Latin word mellitus which means sweet. A review of the history records indicates and shows that the term "diabetes" was first used by Apollonius of Memphis around 250 to 300 BC. Diabetes mellitus (DM) is a metabolic disease, involving inappropriately elevated blood glucose levels. Hemoglobin A1c (HbA1c) is the most extensively used parameter for glycemic monitoring and throw back average glucose levels over 2–3 months. Published research studies have confirmed that GV, especially when related with extreme hypoglycemia, could be harmful not only to people with diabetes but also to non-diabetic patients in critical care settings. The attention dedicated to GV is derived from the above proof regarding concerning its effects on oxidative stress and, from the latter, on chronic diabetes complications. Control of GV has been the focus of a number of interventional studies aimed at reducing this fluctuation. Diet and weight lowering are the first and initial therapeutic instrument that can be used for decreasing GV. The current article reviews the clinical perspectives of GV and understanding its role toward contribution of glycemic control in diabetic patients.

KEYWORDS: Glycemic Variability, HbA1c, Diabetes mellitus.

INTRODUCTION

Diabetes mellitus word is came from the Greek phrase diabetes, that means siphon - to pass through and the Latin word mellitus which means sweet. A review of the history records indicates and shows that the term "diabetes" was first used by Apollonius of Memphis around 250 to 300 BC.[1] Diabetes mellitus (DM) is a metabolic disease, involving inappropriately elevated blood glucose levels. DM has several number of categories, such as type 1, type 2, maturity-onset diabetes of the young (MODY), gestational diabetes, neonatal diabetes, and secondary causes due to endocrinopathies, steroid use, etc. The main subtypes of DM are Type 1 diabetes mellitus (T1DM) and Type 2 diabetes mellitus (T2DM), which classically result from defective insulin secretion (T1DM) and/or action (T2DM). T1DM presents in children or adolescents, while T2DM is thought to affect middle-aged and older adults who have long time hyperglycemia because of poor lifestyle and dietary choices. Glycemic variability (GV), which refers to swings in blood glucose levels, has a broader meaning because it alludes suggest to blood glucose oscillations that occur throughout the day, including hypoglycemic periods and postprandial increases, as well as blood glucose fluctuations that occur at the same time on different days. The broadwide definition of Glycemic Variability considers the intraday glycemic excursions, including episodes of hyperglycemia and hypoglycemia.[2] Glycemic monitoring is imperative for the management of type 2 diabetes mellitus, and various glycemic markers are available in clinical practice.[3]

Hemoglobin A1c (HbA1c) is the most extensively used parameter for glycemic monitoring and throw back average glucose levels over 2–3 months.[4] However, HbA1c is restricted in its capability to reflect short-term glycemic changes, and it cannot reflect postprandial hyperglycemia and fasting hyperglycemia separately.[5]

A developing body of evidence recommended that postprandial hyperglycemia and glycemic variability can also be independent risk factors for macrovascular complications in sufferers with diabetes.[6] Even sufferers with well-controlled diabetes who have HbA1c level

stages beneath 7% (53 mmol/mol) may also be problem to glycemic variability and postprandial hyperglycemia.[7] For extra superior management to stop chronic complications, it is crucial to display a range of various glycemic parameters. However, HbA1c levels may additionally now not effectively reflect hyperglycemic excursions that are compensated for by hypoglycemia, something that is not noted by most clinicians. A continuous glucose monitoring system (CGMS) is the most dependable and particular approach method for evaluating glycemic variability and postprandial hyperglycemia; however, it is inconvenient and not easily accessible in general practice. 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 excessive blood glucose exposure rather than consistent excessive blood glucose exposure has been shown to have deleterious effect in experimental research studies.[8,9,10,11,12] Physicians in their day to day practice, make use of quantitative values of glycemic parameters such as fasting, postprandial blood glucose, and glycated hemoglobin (HbA1C). The current article reviews the clinical perspectives of GV and understanding its role toward contribution of glycemic control in diabetic patients.

The broad wide definition of Glycemic Variablity takes into account the intraday glycemic excursions including episodes of hyperglycemia and hypoglycemia. The postprandial hyperglycemic excursions toomake a contribution to Glycemic Variablity. The incidence of a various number of microvascular and macrovascular complications issues in diabetes is attributed by means of a variety research studies to hyperglycemia and dysglycemia (peaks and nadirs).[13,14,15,16,17] Several pathophysiological mechanisms had been put forward,[18,19] unifying the two main most important mechanisms: Excessive protein glycation end products and activation of oxidative stress in the causation of vascular complication respectively.[20,21]

PATHOPHYSIOLOGY OF GLYCEMIC VARIABILITY

According to various research studies, the prevalance of quite a number of various microvascular and macrovascular complications in diabetes is attributed to hyperglycemia and dysglycemia (peaks and nadirs). Several pathophysiological mechanisms have been reported, unifying the two most important primary mechanisms: excessive protein glycation end products and activation of oxidative stress, which causes vascular complications. Intermittent excessive blood glucose exposure, rather than constant exposure to excessive blood glucose, has been shown and proven to have deleterious outcomes in experimental research studies.[22] In vitro and in vivo data have introduced the mechanisms that are at the basis of the adverse Cardiovascular effects of glycemic variability, which are mainly commonly related with oxidative stress; the atherogenic action of postprandial glucose (PPG) additionally involves insulin sensitivity, the postprandial increase of serum lipids and the glycemic index of food.[23] In In vitro experimental settings and in animal studies, glycemic fluctuations shows a greater deleterious impact on the parameters of CV risk, such as endothelial dysfunction.[24] There is a high affilication association between GV and the elevated incidence of hypoglycemia.[25] Hypoglycemic activities might also trigger inflammation by inducing the release of inflammatory cytokines. Hypoglycemia additionally induces extended platelet and neutrophil activation. Thesympathoadrenal response through hypoglycemia elevated adrenaline secretion and may additionally result in arrhythmias and elevated the cardiac workload. Underlying endothelial dysfunction leading to decreased vasodilation may additionally contribute to CV risk.[26] Published research studies have confirmed that GV, especially when related with extreme hypoglycemia, could be harmful not only to people with diabetes but also to non-diabetic patients in critical care settings.[27] Overall, the pathophysiological proof and evidence appears to be fairly suggestive of GV being an vital important key determinant of vascular damage.[28,29]

GLYCEMIC VARIABILITY: CAN WE PREVENT IT?

This question is a subject challenge of debate. The answer is probably yes, provided that the glucose variability is measured in interventional trials as well as in clinical practice. At present, most of the interventional trials using the “treat-to-target” concept have been performed to achieve near-normal glucose value at fasting and A1C levels <7%.[21] Postprandial and acute glucose fluctuations have rarely or never been taken into account. For this reason, it is hard and difficult to estimate whether glucose variability can be decreased or not. To achieve inaddition perception further insight into this problem, two examples can be considered. Both concern the treatment of sufferers with type 2 diabetes.

CAN WE PREVENT GLUCOSE VARIABILITY BY USING LONG-ACTING INSULIN ANALOGS?

In the LANMET (Lantus Metformin) study[30], the authors validated that in insulin-naive type 2 diabetic sufferers who were not sufficiently managed on oral antidiabetic agents, the implementation of a therapeutic strategy of combining either insulin glargine or NPH insulin with metformin resulted in similar improvements in A1C from baseline to end point at week 36. The mean A1C level dropped by ~2%, from 9% at baseline to 7% at end point in both groups. The eight-point glycemic profile was shifted downward, with the glycemic patterns exhibiting equal-sized changes from baseline to end point at different moments in the day, i.e., at fasting, interprandial, and postprandial time points. As a outcome and even though the glucose variability was once no longer examined in this study, it looks from the glucose patterns that glucose variability remained unchanged and

it can as a result be concluded that the addition of a bedtime insulin dose failed to adjust the acute glucose fluctuations from peaks to nadirs, whatever the type of insulin used, long or intermediate acting.

CAN WE PREVENT GLUCOSE VARIABILITY BY USING GLUCAGON-LIKE PEPTIDE 1 AGONISTS?

In sub-optimally managed sufferers with type 2 diabetes who have been in addition dealt with once-daily injection of insulin glargine.[31] Observed that the changes in A1C and glycemic profiles had been comparable to those obtained.[32] In the LANMET study. In Heine's study[33], the glucose variability was not quantified, however the glucose fluctuations regarded to continue to be unchanged from baseline to end point in the glargine-treated group. In the second group (i.e., in sufferers had been handled with exenatide, a glucagon-like peptide 1 agonist), the authors located that the enhancement in A1C was the same as in the glargine-treated group. However, compared with the insulin glargine group, and everything else being equal in terms of glycemic disorders, the exenatide group exhibited less glucose variability at end point. As in the LANMET study, the magnitude of the glucose excursions was once no longer quantified.[34] However, through studying the crude variation between postprandial peaks and interprandial nadirs on the mean glucose patterns, it apperas that the glucose variability used to be decreased by means of ~50% when the exenatide group was compared with the glargine group. Such data propose that the implementation of treatments aimed at lowering postprandial excursions is actually a precious approach for lowering the parameters that represents the dysglycemia of diabetes (i.e., glycemic disorders issues both at fasting and during postprandial periods) and glycemic variability.[35]

Glycemic variability is a necessary as HbA1c. The type 1 diabetes sufferers in DCCT intensively treated group had lesser microvascular complications issues than conventionally treated group. HbA1c variability was once proposed to give an explaination for the improvement of retinopathy and nephropathy in conventional group.[36] The positive association with cardiovascular risk factors, supports the possibility of relationship between glucose variability and cardiovascular morbidity and mortality.

Most studies have shown proven strongest correlations between A1c and mean plasma glucose levels and it is identified as dependable marker in glycemic stability and its direct consequence, an excess rate of glycation.[37,38,39] However, there are different other mechanisms in the improvement of diabetic complications and the fact that it is the exposure of glucose, which is measured with the aid of 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.[40,41] The common average derived value which consiat of GV might explain in diabetic complication of hypoglycemia with near normal HbA1c in the DCCT group.

MEASUREMENT OF GV: METHODS AND THEIR LIMITATIONS

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

M-value

Developed by[42] in 1964 using six self-monitored blood glucose (SMBG) per 24 hr. The ideal perfect glucose initially proposed was 120 mg/dl and in final formulae it was left to investigator, making it hard and difficult to compare different research 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[43] using hourly obtained blood glucose values over 48 hr. Mean glucose value rather than the ideal glucose is referred to by means of summating absolute rises and falls encountered in a day. Continuous glucose monitoring makes use of Mean amplitude of glycemic excursions (MAGE).

Continuous overlapping net glycemic action

Proposed by[44] it is a continuous glucose monitoring (CGM)-based intraday GV. The Standard deviation (SD) of summated variations 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 once proposed by[45] taking into mean absolute value differences of glucose of two consecutive days at the same time. It used to be developed the use of hourly blood sample during 48 h. It ignores excursions of less than 1 SD.

Standard deviation

It is the easiest method using 7 point SMBG. However, it can miss certain peaks and nadirs happening in between readings. The inter day variation can additionally be calculated through SD of fasting glucose concentrations.[46] and is a measure of long-term glucose variability, however 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, however in daily practice it turns to difficult.

Thus in search for glucose stability, the glycemic excursions had been taken into consideration from middle of the 20th century putting forward more than a few measuring parameters, mean glucose values in comparison to ideal glucose,[47] measuring glycemic excursions,[48] 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.[49,50] Risk of daily GV is not expressed by SD or CV. To overcome this, suggested that low and high blood glucose indice (LBGI and HBGI) and average daily risk range (ADRR) parameters derived from SMBG[51] to address the risk of GV.

MEASURES OF MINIMIZE GV

Life style measures

Diet-induced weight loss can notably enhance no longer solely insulin sensitivity however additionally β-cell function, capable of decreasing glucose levels and delaying the progression from impaired glucose tolerance (IGT) to diabetes.[52,53] Recently a research study on diet of high glycemic meal with pistachio nuts has shown blunted postprandial response. The study find out 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 had been determined to be extensively decreased 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.[54] It used to be 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.[55,56,57] showed that controlled-release glipizide combined with acarbose was once greater more effective in lowering MAGE than controlled-release glipizidemonotherapy.

Glimepiride logically must reason less GV than glibenclamide. Extra pancreatic effect, rapid association, and dissociation binding properties with receptors and effect on both phases of insulin secretion in sufferers with type 2 diabetes are the feasible mechanisms.[58,59] The insulin-releasing activity is excessive with glibenclamide and lowest with glimeperide.[60]

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 manufacturing is no longer suppressed during times of prandial glucose consumption main 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 regular physiological insulin response to meals. Prandial dosage premits 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 managed on oral agents in obese randomized type 2 diabetic sufferers suffering for a goal fetal bovine serum (FBS) ≤100 mg/dl, had better glycemic control with lower episodes of hypoglycemia.[61] It used to be attributed to better GV in the glargine group. The 8-point self-monitored glucose profile confirmed much less inside subject variability of FBG.

In an another study LANMET[62] the mean A1c level dropped with the aid of 2% from base line to end point, it was once commented that glucose variability remained unchanged, and addition of a bed time insulin dose failed to regulate the acute glucose fluctuations from peaks to nadirs, whatever the type of insulin used.

Basal bolus insulin therapy

An alternative choice to basal bolus insulin therapy to provide constant 24 h base line insulin and covering meal time glycemic excursions as stated mentioned above, near mimicking to endogenous insulin availability with premixed 50/50 mealtime plus metformin in type 2 diabetes sufferers who were on 0–2 insulin injections per day were studied by[63] The overall HbA1c levels and preprandial blood glucose and PPBG were lower (except FBG) with similar reduction in nocturnal hypoglycemia and low GV, compared with Glargine and Metformin.

Continuous subcutaneous insulin infusion in intensive management

With more use of CGM system GV was once greater evident in sufferers with similar HbA1c levels. (CSII) Continuous Subcutaneous Insulin Infusion used to be regarded as alternative when glycemic manage was not achieved with use of multiple dose insulin regimen in Type 1 diabetic patients.[64] Use of CGM itself in self-management in T1DM has been found to have decreased MAGE by means of 10%, SD, hyperglycemic time,

hypoglycemic time, and significant effect on QoL.[65] observed that improvement of glycemic control after CSII was related 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.[66,67]

GLP-1 analogues

Glucose-dependent insulinotropic peptide (GIP) and GLP-1 activation of incretin receptors on β-cells will increases insulin release in response to glucose and has additional benefits of enhanced glucose disposal in peripheral tissues and protection against ischemia/reperfusion injury.[68,69] In critical care setting, glucose variability is a predictor of mortality and was once set as important goals in glucose management in intensive care unit (ICU). MAGE a measurement of GV was found to be decrease in sufferers receiving exenatide in severely burned pediatric patients.[70] and resulted in a decreased 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.Exenatide had better effect on decreasing GV when compared with glimerpiride treatment. The benefits imparted by exenatide should be defined via glucose dependent stimulation of insulin secretion and concomitant suppression of glucagons.[71]

DPP-1 V inhibitors

Vildagliptin, Sitagliptin, Saxagliptin, and other different DPP-IV inhibitors increase endogenous GIP and GLP-1 by means of inhibiting their degradation. Gliptins had been encouraged as a monotherapy or add on therapy in drug naive type 2 diabetes. There used to be a widespread reduce 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 enhancement in β-cell characteristics function over 2 year treatment period.[72] The study examined influence of 2-year treatment with vildagliptin (50 mg once daily) on glycemic control and B-cell function in sufferers with T2DM and mild hyperglycemia. In the same study observation of lower hyperglycemia period during 1 year treatment period and increase in 4 week wash out period explains that glycemic manage is closely regulated with glycemia state and β-cell responsiveness. Sitagliptin drastically decrease blood 2 and 24 h AUC, MBG, and reduction in time spent in euglycemic range in adult patients with T1DM.[73]

Modified bariatric surgery with ileal interposition

Metabolic surgery operation is a novel procedure done mainly in obese sufferers with poor glycemic control in T2DM.[74,75,76] We have previously demonstrated that even nonobese subjects with poorly controlled diabetes on oral hypoglycemic agents (OHA)/insulin have been discovered to have better glycemic control without any requirement of exogenous insulin after ileal interposition with sleeve gastrectomy/ diverted sleeve gastrectomy.[77,78,79] FBG, PPBG, and HbA1c have significantly improved. It was attributed to rapid stimulation of interposed ileal segment via ingested food leading to augmented GLP-1 secretion.

HOW TO MINIMIZE GLYCEMIC VARIABILITY

The attention dedicated to GV is derived from the above proof regarding concerning its effects on oxidative stress and, from the latter, on chronic diabetes complications. Control of GV has been the focus of a number of interventional studies aimed at reducing this fluctuation. Diet and weight lowering are the first and initial therapeutic instrument that can be used for decreasing GV. Glucagon-like peptide-1 analogs and dipeptidyl-peptidase 4 inhibitors demonstrated a widespread influence on GV in people with T2DM. Regarding insulin therapy, the evolution of fast-acting and long-acting insulin has had a positive impact on the control of GV. One of the aims of the ultraslow analog degludec, which was recently approved for clinical use, is to reduce GV by virtue of its smaller pharmacodynamic variability. To date, the published posted outcomes exhibit that degludec is capable of decreasing the frequency of episodes of hypoglycemia in sufferers with T1DM and postprandial glycemia oscillations in sufferers with T2DM, suggesting potential efficacy in the control of GV. Continuous Subcutaneous Insulin Infusion (CSII) and bariatric surgery had been additionally related with considerable rate reductions in hyperglycemic excursions along with the mean glucose. Lastly, the development of new technologies for diabetes education, monitoring and therapy, particularly in T1DM, has made it possible to identify GV as anrising goal for enhancing overall diabetes treatment. There have to be no doubt that pharmacological advances directed at the ultimate goal of physiological insulin replacement will continue to the point where the postprandial glycemic curve will be bent to conform to that of nondiabetic subjects. In that ideal situation, the currently present available measures of GV can be retired.[80]

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 ought to be relevant to all T1DM, T2DM, gestational diabetes, and probably non-diabetic critically ill sufferers. Studies have shown improved outcomes for micro and to some extent macrovascular diabetic complications by minimizing GV. Inspite of various formulas offered, simple and standard clinical tool to define GV is yet to evolve. Current diabetes medicines like incretinmimetics, newer basal and prandial insulins, CSII and modern bariatric surgical techniques in obese type 2 diabetic patients significantly reduce GV.

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