An update on glycaemic variability: clinical and therapeutic implications

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Abbreviations: AKT: protein kinase B, AUC: aria under the curve, CGM: continuous glucose monitoring, CONGA: Continuous Overlapping Net Glycaemic Action, CSII: Continuous Subcutaneous Insulin Infusion, CV: coefficient of variation, DPP4i: dipeptidyl-peptidase 4 inhibitor, FPG: fasting plasma glucose, GLP-1RA: glucagon-like 1 receptor agonist, GV: glucose variability, HBGI: High Blood Glucose Index, ICU: intensive care unit, IDeg: insulin degludec, IGlar100: insulin glargine 100 U/mL, IGlar300: insulin glargine 300 U/mL, IQRs: Interquartile Ranges, LBGI: Low Blood Glucose Index, MAGE: mean amplitude of glucose excursions, MDI: multiple daily

injections, MODD: Mean Of Daily Differences, PPG: post-prandial glucose, SGLT2i: sodium-glucose cotransporter 2 inhibitor, SD: standard deviation, SMBG: self monitoring blood glucose, T1D: type 1 diabetes, T2D: type 2 diabetes.

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Abstract

Glucose variability (GV) is an integral component of glucose homeostasis although as yet not fully endorsed as an independent risk factor for long-term diabetic complications. However, it can represent the presence of excess glycaemic excursions and consequently the risk of hyper- or hypoglycaemia. At present GV is defined according to an ever increasing number of metrics representing either short- or longer-term GV and is aimed at being incorporated into clinical practice. In the meantime, short-term within-day GV, with a coefficient of variation at 36% separates stable from labile glycaemic control. In contrast, longer-term GV is usually based on quarterly visit-to-visit measurements of HbA1c or other measures of glucose homeostasis. The relationship between GV and diabetes related complication predominantly from the recent literature is reported in this review along with reference to a number of non-pharmacological and pharmacological strategies (GLP-1 receptor agonists, SGLT-2 inhibitors, new long-acting insulins and also their fixed combinations with GLP-1 receptor agonists), which are presently available to address this challenging aspect of diabetes management.

Introduction

Diabetes care management strategies from a *"glucocentric"* perspective should aim to address the three main components of dysglycaemia, i.e chronic hyperglycaemia, hypoglycaemia and glycaemic variability (GV).[1] These features contribute to the development and progression of diabetic complications.[2] Long-term interventional

trials comparing intensive with standard management of diabetes, have clearly demonstrated the association between prolonged poor glycaemic control and the development especially of microvascular and, to a lesser extent, macro-vascular complications.[3,4]. During the last decade, the deleterious effects of both short-term GV (within-day glucose fluctuations, peaks to nadirs), and long-term variations utilising fasting plasma glucose (FPG) and HbA1c have been proposed[5,6] although definitive evidence on hard outcomes remains limited.[7] It is now realised, however, that the availability of glucose monitoring, especially continuous glucose monitoring (CGM), is of considerable value for making management decisions, whereas on the other hand HbA1c used in isolation can be misleading.[8] Short-term GV is of increasing concern for health care professionals intent on preventing excessive upward and downward fluctuations of glucose, with the potential risk of precipitating episodes of hyperglycaemia or hypoglycaemia respectively,[6] with a negative impact on patients' quality of life.[9] Short or longer-term GV also appear to be associated with increased episodes of severe hypoglycaemia resulting in adverse cardiovascular outcomes and all-cause mortality.[10,11] However, definitive evidence for the role of GV in the genesis and severity of chronic adverse clinical outcomes in persons with diabetes is still lacking compared to that of chronic glucose exposure, depicted by HbA1c.[2–4]

Therefore, the aim of this article is primarily to review the relative large number of publications that have appeared during the last three years (2015 and onwards), but also to refer to the landmark studies published earlier, that address the issue of GV and diabetes complications. Clinically the relationship between GV and diabetes complications is presently not easy to establish due to heterogeneity between the studies including their design and especially the different metrics used to assess GV. Additionally, most antidiabetic treatments impact on components of the glycaemic 'triumvirate' (ambient hyperglycaemia, GV and hypoglycaemia) to different degrees.[1, 12–16] Individualising care ('precision' medicine) based on daily continuous glucose profiles and GV is the eventual glycaemic objective. However, it should be acknowledged that such an objective might take a long time.

Literature search strategy

- Literature searches were completed for the terms “glycaemic variability”, “glucose variability”, “fasting glucose variability”, “HbA1c variability”, “glucose fluctuation” and “oscillating glucose”. Database used was PubMed.
- References retrieved were reviewed and selected manually according to their relevance to the aims of this review. Except for the key historical references on the topic, priority for inclusion has been given to relevant literature published in the last 3 years (2015 and onwards).

Metrics of glycaemic variability: does profusion create confusion?

GV is usually defined by the measurement of fluctuations of glucose or other related parameters of glucose homeostasis over a given interval of time. This description covers two predominant categories of measurements (Table 1): (a) “short-term” GV represented by both within-and between-day GV and (b) “long-term” GV based on serial determinations over a longer period of time, usually involving HbA1c, but also serial FPG and postprandial glucose (PPG) measurements. However, the acceptance and clinical relevance of this proposed classification remains a subject of debate. For many years, short-term GV was calculated from self-monitoring of blood glucose (SMBG) measurements[7], but this method is being progressively replaced during the last past few years by continuous glucose monitoring (CGM).[17,18] SMBG at best provides an abbreviated diurnal blood glucose profile[19] whereas CGM with interstitial glucose measurements at 5 minutes-time intervals is a more comprehensive record covering the day and night time periods and regarded as the gold standard method for assessing short-term GV.[17,18] Fleisher and colleagues also recently reported a poor correlation ($R2 = 0{\cdot}26$, $p< 0{\cdot}05$) between the mean amplitude of glycaemic excursion (MAGE) obtained from structured SMBG testing and those computed from CGM.[19] However, structured SMBG provides the possibility to determine the two main components of short-term GV ie: the “within- and between-day” GV. Traditional measures of within-day GV include either or both the standard deviation (SD) and derived coefficient of variation (CV). When averaging each daily SD or CV the “mean of within-day daily” GV over the stated period of time can also be estimated.[20] Another method is to calculate the SD from the averaged glucose profiles, which is called the “daily SD by average”. This estimate is usually smaller than the “mean of within-day daily SD”, with the underestimation exaggerated when the glucose

patterns from day-to-day becomes more different. A large disparity between these two indices reflects a high degree of between-day GV.[21]

The metrics considered the best for estimating the between-day GV is the MODD (Mean Of Daily Differences)[21] which was introduced in the early 1970's by Molnar and colleagues.[22] The computation is based on the calculation of the absolute differences between two glucose values measured at the same time within a 24-h interval with a high MODD score indicative of a large between-day GV. This metrics is not currently provided with the available CGM devices thus requiring additional computation.

An additional parameter of GV is the dispersion of the glucose data at given time-points over several consecutive days employed by the Flash monitoring system the Free Style Libre, which computes the "Averaged Glycaemic Profile" over a defined period of 14 days with the results reported as Interquartile Ranges (IQRs).[23] A high IQRs indicates a loss of synchrony of glucose patterns from day-to-day, i.e. a high between-day GV whereas a low IQRs implies little between-day GV.[20,21]

Other more complex metrics are also available for assessing short-term GV, but are rarely applied in routine clinical practice and are reported in the Table 1.

Although we have mainly focused on the metrics of GV based on the SD, whilst omitting the more complicated computations, the output can still remain somewhat difficult to interpret. Therefore, simplifying the message is a prerequisite for healthcare providers to easily calculate and interpret short-term GV. We recently proposed the coefficient of variation (CV) as the most appropriate index for assessing mean within-day daily GV and which is independent of the mean glucose concentration with a cut-off threshold value of 36% separating stable from labile glycaemic control.[6] Although the attributed level of evidence for this threshold has been graded as E (Expert consensus of clinical evidence using the grading system developed by the ADA), it has recently been adopted by the International consensus on the use of continuous glucose monitoring [18]. A few years earlier based on personal observations a threshold value equivalent to a CV of 33% was suggested by Hirsch [24] as an ideal target derived using the following formula: SD x 3/ mean glucose. Some experts express the difficulty in defining a meaningful threshold for short-term GV in order to differentiate labile from stable diabetes. However, it should be remembered the difficulties encountered in arriving at clear recommendations for HbA1c that separate satisfactory from unsatisfactory diabetes control and for the

definition of hypoglycaemia [25]. As described in our original publication we chose to consider as a reference for stable diabetes a group of persons treated only with dietary measures and/or insulin sensitizers, with a minimal risk of hypoglycaemia, and defined the threshold between stable and unstable diabetes as the upper limit of the distribution of CV in this group.

The second type of GV, namely long-term GV, is usually based on visit-to-visit measurements of HbA1c, FPG or PPG,[26] with the subsequent calculation of their SD and CV. The long-term GV is in part a reflection of the ambient hyperglycaemia because measures of long-term variability correlate with either mean blood glucose concentrations (r = 0·73)[7] or mean HbA1c (r = 0·55).[27] As mentioned by others it is highly likely that this definition of long term variability is an umbrella term that encompasses different concepts and definitions [28 Noyes et al Diabetic Medicine 2018;36:262-269 NOTE a new reference]

The current lack of consensus on the metrics to describe both short-term and long-term GV partly contributes to difficulties in establishing the relationships between them and clinical outcomes.

Table 1 attempts to represent a simplified view of the different metrics of GV available, summarising their outcomes (interpretation), advantages and limitations.

Mechanisms

Two historical in vitro studies showed that short-term (4 days) and longer-term (21 days) glucose oscillation enhanced human tubule-interstitial cell growth and collagen synthesis[29] and accelerated apotosis in human umbilical vein endothelial cells [30] more than exposure to a constantly high glucose level. Shortly afterwards, it was shown that oxidative stress was the key player in producing damage to endothelial cells.[31] Several other studies have since confirmed that oscillating glucose, via oxidative stress, can adversely affects cells of different organs.[32] More recently the source and the targets of oxidative stress during glucose fluctuation have been further characterized. The mitochondrion is still considered the key player in inducing superoxide production during GV, together with NADPH oxidase.[33,34] Most recently, the involvement of the AKT pathway in this process has also been recognised.[35] Blood glucose fluctuation accelerates renal injury involving inhibition of the AKT signalling pathway in

diabetic rats.[36] GV can also induce increased chromatin remodelling[37] which, can play an important role in GV- induced "metabolic memory".[38]

Human's studies are less consistent with some showing that oxidative stress is produced during GV [1,39] and that oscillating glucose is more deleterious to endothelial function via oxidative stress than mean glucose in subjects with or without and type 2 diabetes (T2D).[40] Other studies were unable to confirm that short-term GV was associated with raised oxidative stress markers in healthy volunteer[41,42] and type 1 diabetes (T1D).[42] As insulin has an inhibitory action on inflammation, thrombosis and activation of oxidative stress, the possibility that insulin affected the results, in positive or negative way, cannot be excluded.

Intriguingly, it has been recently reported that in T2D in remission after bariatric surgery, there is an increased GV, which is accompanied by an increase in oxidative stress.[43]

Evidence also exists that hyperglycaemia after recovery from hypoglycaemia worsens endothelial function and increases oxidative stress and inflammation in healthy control subjects and subjects with T1D. This does not appear when recovery from hypoglycaemia is followed by normoglycaemia.[44]

Glucose variability: hard outcomes in persons with and without diabetes

Pre-2015 several studies have reported a positive association between GV and diabetic complications, both macro- and micro-vascular.[32] In the last three years new evidence has appeared in support of GV being an independent risk factor for total mortality and death due to cardiovascular disease in both T1D and T2D.[26, 45–49]

GV increased recurrent cardiovascular events and mortality in persons with diabetes following episodes of acute ischemic stroke.[50] An elevated GV is significantly associated with 3-month cardiovascular composite outcome, with increased cardiovascular outcomes in the highest GV quartile similar in both euglycaemic and hyperglycaemic groups. Moreover, a very recent study reported a strong association between long term GV and mortality in old patients with diabetes.[51] It is of considerable interest that within day GV evaluated by CGMS is associated with the 10-year cardiovascular risk in well-controlled diabetic patients based on HbA1c.[52]

These data are consistent with the evidence that indicate short-term GV may adversely affect diabetes plaque stability,[53] subclinical coronary atherosclerosis[54] and extends QTc duration and dispersion.[55] More recently, longer-term HbA1c variability

has been associated with a higher risk of developing atrial fibrillation[56] and the incidence of heart failure.[57] Moreover, reducing GV with insulin via continuous subcutaneous infusion is accompanied by an increase in circulating endothelial progenitor cells in T1D.[58]

Similarly, long-term GV (HbA1c) in T2D has been associated with the risk of developing diabetic nephropathy.[59,60]

Also an association between long-term GV (HbA1c) and diabetic retinopathy has been demonstrated in some studies with T1D.[61,62] GV causes inner retinal sensory neuropathy in persons with T1D.[63] However, no association was seen between short- or long-term GV with progression of microvascular outcomes in T1D in the Diabetes Control and Complications Trial.[7]

GV seems also to be a risk factor for diabetic neuropathy, and not only in terms of retinal neurodegeneration,[61] but particularly in terms of polyneuropathy and cardiovascular autonomic neuropathy in persons with T2D.[64,65] A reduced cardiac autonomic modulation is evident in women with T2D with high GV.[66]

There is also considerable interest for the emerging association between GV and the decline of cognitive function.[67,68] HbA1c variability appears to predict symptoms of depression in elderly individuals with T2D,[69] including the risk of developing the Alzheimer disease.[70] It has also been suggested that repetitive GV at brain level may produce "relative cerebral hypoglycaemia",[71] which can induce neuroglycopenia with further impairment of cerebral blood flow, paving the way for a recurring pattern of hypoglycaemia, hypoglycaemia unawareness, and associated neuropathology with cognitive dysfunction.

As anticipated, even cumulative evidence suggest a role for GV in diabetic complications, there are also studies to the contrary. Recently, a post-hoc analysis from the DCCT assessed the association of GV within and between quarterly 7-point glucose profiles with the development and progression of retinopathy, nephropathy, and cardiovascular autonomic neuropathy.[7] Measures of variability included the within-day and updated mean (over time) of the SD, MAGE, and M-value, and the longitudinal within-day, between-day, and total variances. Adjusted for mean blood glucose, no measure of within-day variability was associated with any adverse outcome.

When GV has been evaluated as risk factor for complications in the DCCT the results have been predominantly negative, but also inconsistent with HbA1c variability

associated with increased risk of retinopathy.[72] Limitations of the current studies, as underlined by the same authors of the DCCT, include a reliance on seven-point SMBG profiles at quarterly intervals to represent the mean blood glucose concentrations and variability over time.[73] Such infrequent measurements can therefore lead to erroneous measures of GV.[73]

An interesting aspect of GV is its impact in people without diabetes. GV is an independent risk factor for a worse outcome in several acute conditions[74] although when corrected for other confounding variables this association can be lost.[75] However, a meta-analysis indicated that GV remains a risk factor even when correcting for several confounding variables: (severity of illness expressed as APACHE II score), the overall blood glucose level (expressed as the mean blood glucose of the entire stay of the patient in the intensive care unit [ICU]); blood glucose measurement frequency (expressed as the mean interval between measurements); having at least one severe hypoglycaemia event (< 40 mg/dl blood glucose level).[76]

GV also seems to indicate an increased risk of a major cardiovascular event after 30 days following acute coronary syndrome,[77] isolated cardiac valvular surgery[78] and intracerebral haemorrhage.[79] More recently, GV has also been associated with higher risk of mortality in the general population.[80]

Interestingly, increased GV has been found to be strongly associated with mortality in ICU in persons without diabetes, but less so in those with diabetes.[81] Similarly, a poorer 30-day functional outcome following acute intracerebral hemorrhage was observed in those without diabetes and increased GV.[79]

In those persons with an HbA1c > 8·5%, increasing GV was not associated with increased mortality.[82] Hypoglycaemia was also associated with mortality, but prior exposure to hyperglycaemia had a lesser effect on this relationship. As a hypothesis, previous exposure to hyperglycaemia may act as a “preconditioning” factor, minimizing the effect of GV.

It should be acknowledged that at present we are sadly lacking of any long-term interventional study providing compelling evidence for a beneficial effect of reduction in short-term GV on hard outcomes such as the development and progression of micro- and macro-vascular diseases. Firstly, in all studies aimed at attenuating the magnitude of GV or of postprandial excursions, the tested group and its comparator were submitted to pharmacological interventions using different treatment regimens

but always with at least one insulin preparation in both groups. For instance, the Heart 2D Study[83], was initially designed to answer whether control of basal or prandial hyperglycaemia is best for reducing cardiovascular outcomes in poorly controlled T2D. Patients were assigned to either a basal insulin strategy or an insulin regimen with 3 daily injections of rapid insulin-acting analogues at pre-meal times. Therefore, it appears that both groups were treated with insulin. At the end of the study, almost all people were anyhow treated with both basal and prandial insulin and, even statistically significant, the difference in postprandial hyperglycaemia during the study was not that predefined in the study.[83] Interestingly, in a post-hoc analysis a beneficial effect on reducing post-prandial hyperglycaemia was reported in oldest people and in people with a longer duration of the disease.[84]

The same remark can be applied to the FLAT-SUGAR study[13] that was designed to test whether an add-on therapy with exenatide to an on-going basal insulin regimen can reduce short-term GV and improve cardio-metabolic risk markers. The albuminuria, serum C reactive protein, serum interleukin-6 and urinary prostaglandin F2ά, were also similar in the two treatment strategies. The difference in GV was relatively small and the duration of the study was very short and both groups were on insulin treatment. Insulin has an inhibitory action on inflammation, thrombosis and activation of oxidative stress,[85] and therefore one can hypothesise that the potential benefit of reducing GV or postprandial excursions may not be apparent due to the predominant response to insulin per se. The second difficulty lies in the fact that most antidiabetic therapies exert their effects on diabetic control via a concomitant reduction in both ambient hyperglycaemia and GV[13]. As a consequence, the ideal randomized intervention trial for testing the specific impact of reducing GV on cardio-metabolic risk markers and beyond (hard cardiovascular outcomes) should avoid the use of insulin treatment in the comparator groups[86] and aim to achieve a similar degree of ambient hyperglycaemia in those with or without improvement in GV. Finally, one can anticipate difficulty in conducting a study with CGM over a prolonged period of time unless suitable wearable devices became available. According to these remarks it is questionable whether such trials are technically, financially and ethically feasible. For all these reasons, *in vitro* experiments on cells or in vivo experimental studies in animals and humans therefore provide at present the best opportunity for investigating the potential deleterious role of abnormally high GV despite the many obvious limitations.

Relationship between glycaemic variability and hypoglycaemia

Achieving near normoglycaemia is a key objective in the management of diabetes, which is well supported by observational, epidemiologic and several interventional studies confirming the relationship with cardiovascular events, premature death and microvascular complications.[87]

Unfortunately, the maintenance of normoglycaemia over a lifetime of diabetes is a major challenge whilst also attempting to avoid hypoglycaemia.[88] In 2000, the authors of the Action to Control Cardiovascular Risk in Diabetes Study Group (ACCORD) demonstrated that striving to achieve a too stringent glycaemic goal (HbA1c < 6%, 42 mmol/mol) with intensive therapy resulted in increased frequency of hypoglycaemia although not causally related to increased risk of cardiac death.[89] Therefore, the principle should be to achieve the best glycaemic control whilst limiting the risk of hypoglycaemia. Such a strategy will, however, increase the risk for the development or progression of micro-angiopathic complications, especially when applied to younger patients with a long life expectancy. It is also important to be aware that excessive short-term GV, even in the presence of target HbA1c levels, can contribute to the risk of hypoglycaemia. This risk is more likely when the mean blood glucose is low or if deviations around the mean glucose values are large,[90] advocating the need to reduce short-term GV. The role of acute glucose fluctuations as a risk factor for hypoglycaemia has only recently been fully demonstrated using CGM technology. In persons with T2D treated with either oral antidiabetic and/or insulin, the mean glucose concentration and its SD were the best variables at predicting the frequency of asymptomatic hypoglycaemia.[91] Incident asymptomatic hypoglycaemia (interstitial glucose value < 3·3 mmol/L, 56 mg/dL) was negatively associated with the mean glucose concentration but positively associated with short-term GV as represented by the SD.[91] Similar findings were observed when analysing 828 day-patient glycaemic profiles (ambulatory CGM) carried out in T1D (331), T2D treated with insulin (216) and non-insulin-treated T2D (222).[92] The three groups were further divided into three subgroups according to whether the 24-hour mean glucose value was < 8·3 mmol/L (<150 mg/dL), between 8·3–10·0 mmol/L (150 and 180 mg/dL) or > 10 mmol/L (>180 mg/ dL). Finally, in each subset, the frequency of hypoglycaemic episodes (interstitial glucose values < 3·3 mmol/L, 56 mg/dL) was compared according to whether the within-day GV (SD around the mean glucose value) was above or below

the mean SD in each selected subgroup which was 3·3 mmol/L (60 mg/dL) in T1D, 2·9 mmol/L (50 mg/dL) in insulin-treated T2D and 1·7 mmol/L (30 mg/dL) in non-insulin-treated subjects (Figure 1). The frequency of hypoglycaemic episodes when ranked according to decreasing ordinal were T1D> insulin-treated T2D> non-insulin-treated T2D and also within each category of diabetes, the frequency of hypoglycaemic episodes increased with decreasing mean glucose values. Importantly, in each subgroup, the frequency of hypoglycaemic episodes increased substantially when the GV exceeded the mean SD value and representing an increased risk for hypoglycaemia. In a similar group of subjects it has been also demonstrated that the incidence of hypoglycaemic events is 3 to 6-fold greater in those with a within-day CV> 36% (referred to as labile diabetes) than in a subgroup with a CV ≤36% (considered to be stable) irrespective of the type of diabetes either T2D treated with oral antidiabetic agents including a sulfonylurea, T2D on insulin or T1D.[6] The mean glucose concentrations were similar across the three groups, confirming that the within-day GV is a key player associated with the incidence of hypoglycaemia.
An additional pending question is to know whether excessive acute glucose fluctuations can exert adverse effects independently of hypoglycaemia. Oxidative stress has been observed in poorly controlled T2D patients (HbA1c levels 9·6%) with acute glucose fluctuations who did not suffer from any hypoglycaemic events.[39]

Glycaemic variability and therapeutic implications

Glucose variability treatment: non-pharmacological options

The HypoCOMPaSS trial suggested a role for education in decreasing GV in subjects with long-lasting T1D with frequent severe hypoglycaemia and the presence of hypoglycaemia unawareness.[93] Moderate physical exercise has been shown to lower GV and reduce oxidative stress in subjects with T2D and impaired glucose tolerance.[94]
Combining CGM with appropriate education appears a promising strategy for improving glycaemic control.[16] In the DIAMOND trial[16] the authors found that persons with T1D using CGM compared with usual care resulted in an improvement in both HbA1c (- 0·6%) and GV (CV- 4%) from a similar baseline value of 42%.
A recent review reported that CGM has beneficial effects on metabolic control (reduced risk of hypo- and hyperglycaemia, decreased GV, mean glucose, and HbA1c

values) in both T1D and T2D undertaking various treatment regimens (either multiple daily injections (MDI) or Continuous Subcutaneous Insulin Infusion (CSII)).[95]

Glucose variability treatment: pharmacological options

Achieving a normal or near-normal HbA1c value without increasing the risk of hypoglycaemia is crucial especially during the early stages of T2D with a HbA1c between 6·5 and 7·5% (47 and 58 mmol/mol) respectively, when dysglycaemia is limited to an exaggerated dawn phenomenon and/or abnormal postprandial excursions.[96] A post-hoc analysis of the OPTIMA study using CGM showed that the dipeptidyl-peptidase 4 inhibitor (DPP-4i) agents sitagliptin and vildagliptin, when prescribed as add-on therapy to metformin in persons with T2D, achieved a reduction of GV (MAGE).[96] A similar effect may be obtained with the sodium-glucose cotransporter 2 inhibitors (SGLT-2i) in T1D.[97,98]

When oral antidiabetic agents fail to achieve or maintain satisfactory glycaemic control, it is necessary to advance towards injectable antidiabetic therapies, the options being between adding a basal insulin or a GLP-1 receptor agonist (GLP-1RA).[99] The addition of exenatide once weekly to metformin in T2D subjects improves glucose control with a significant decrease in FPG, 2h-PPG and GV (MAGE and SD of mean glucose) and increasing the time spent in euglycaemia and less in hypoglycaemia.[100] Similarly, lixisenatide when added to basal insulin therapy significantly decreases the risk of hypoglycaemia and GV.[101] When comparing insulin glargine U100 (IGlar100) with insulin glargine U300 (IGlar300) in T2D, there is no significant change in short term GV except for MODD being lower with IGlar100.[102]

In the DEVOTE trial the cardiovascular safety of insulin degludec (IDeg) was compared to IGlar100 in T2D subjects at high cardiovascular risk.[12] The study demonstrated that IDeg in comparison to IGlar100 at equivalent levels of glycaemic control, lowered episodes of confirmed severe hypoglycaemia by 40% and nocturnal severe hypoglycaemia by 53%. In addition, in a post-hoc analysis of this trial (DEVOTE 2) it was found that a positive correlation existed between the inter-day FPG variability and both the risk of severe hypoglycaemia and all-cause mortality.[10]

When the basal insulin supplementation is deemed insufficient in T2D two further options are currently available, include the addition of a GLP-1RA or a short-acting insulin analogue. There are two randomized studies, the FLAT-SUGAR Trial,[13] and the AWARD-4 substudy,[14] which have assessed the impact of basal insulin in combination with a GLP-1RA on both the ambient hyperglycaemia and GV. The

FLAT-SUGAR trial was a 26-week randomized trial comparing a basal-bolus insulin regimen to basal-insulin with the short-acting GLP-1RA exenatide, injected twice daily before the largest meals. This therapeutic strategy resulted in a reduced short-term GV (CV and MAGE) although the improvement in HbA1c was equivalent in the two therapeutic groups.

The AWARD-4 sub-study[14] in persons with T2D conducted over an initial period of 26 weeks and extended to 52 weeks found that the between-day GV (MODD) was slightly but significantly decreased with the once daily GLP-1RA dulaglutide plus prandial insulin lispro when compared to a basal-bolus insulin regimen of IGlar100 plus prandial lispro. More recently, however, improvements in both ambient hyperglycaemia (% participants within glucose target range 3·9 to 9·0 mmol/L), GV and lowering the risk of hypoglycaemia has been observed when a fixed ratio combination of basal IDeg and the GLP-1RA liraglutide (IDegLira) was compared to either IDeg or liraglutide administered alone.[103]

In summary, it appears clearly that in the management of T2D the incretin-based therapies either incretin-modulators (DPP-4i) at an early stage of the disease or incretin-mimetics (GLP-1RA) at a later stage can reduce concomitantly the ambient hyperglycaemia and the GV without enhancing the risk of hypoglycaemia.

The recent addition of the ultra-long acting insulin preparations can also lower GV, with a reduced risk of hypoglycaemia and providing greater flexibility in dose administration whilst maintaining overall efficacy remains.[104]

Conclusions

With the adoption of blood glucose monitoring, made easier and more meaningful by the availability of CGM, GV is emerging as an additional glycaemic target, even though doubt remains over its role either as short- or long-term GV as independent risk factors for diabetes related complications. The enhanced risk appears related both to the possible vascular damage due to excessive glucose fluctuations and the increased risk of hypoglycaemia and its consequences. Providing health care professionals with such information on GV needs to be limited to indices which can be easily obtained and interpreted, coupled with an awareness of the different lifestyle and therapeutic options available to lower GV safely and without compromising glycaemic control. Currently, limiting the assessment of within-day GV based on the magnitude of the SD and/or the derived CV should limit confusion. It is noteworthy

that the International Consensus of Use of Continuous Glucose Monitoring has recently integrated a CV < 36% as a key metrics of primary GV for defining stable diabetes.[18] Further recent developments of clinical value with CGM includes the Flash monitoring system of Free Style Libre. Future developments in CGM systems and indices for better defining and deciphering glycaemic control including GV and relevance to clinical practice are eagerly awaited in this fast moving and essential segment of diabetes management.

Author Contribution

All Authors contributed equally to literature search, data collection, data analysis, data interpretation and writing the article. Final approval of manuscript: all authors

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Figure 1: Total (symptomatic plus asymptomatic) hypoglycaemic episodes (interstitial glucose concentration< 56 mg/dL) during continuous glucose monitoring expressed as number/patient-day in 3 groups of persons with T1D (figure 1a), T2D treated with insulin (figure 1b) and T2D treated only with diet and oral antidiabetic agents (figure 1c); (Adapted from Monnier, L, Colette, C, Dejager, S, and Owens, DR. Near normal HbA1c with stable glucose homeostasis: the ultimate target/aim of diabetes therapy. Rev Endocr Metab Disord. 2016; **17**: 91–101).

Table 1: List of main metrics developed for assessing glycemic variability. For each index, short notes on computation, interpretation, advantages and limitations are indicated.

Glossary:

SD = standard deviation

CV = coefficient of variation

MAGE = Mean Amplitude of Glycemic Excursions

CONGA = Continuous Overlapping Net Glycemic Acting

ADRR = Average Daily Risk Range

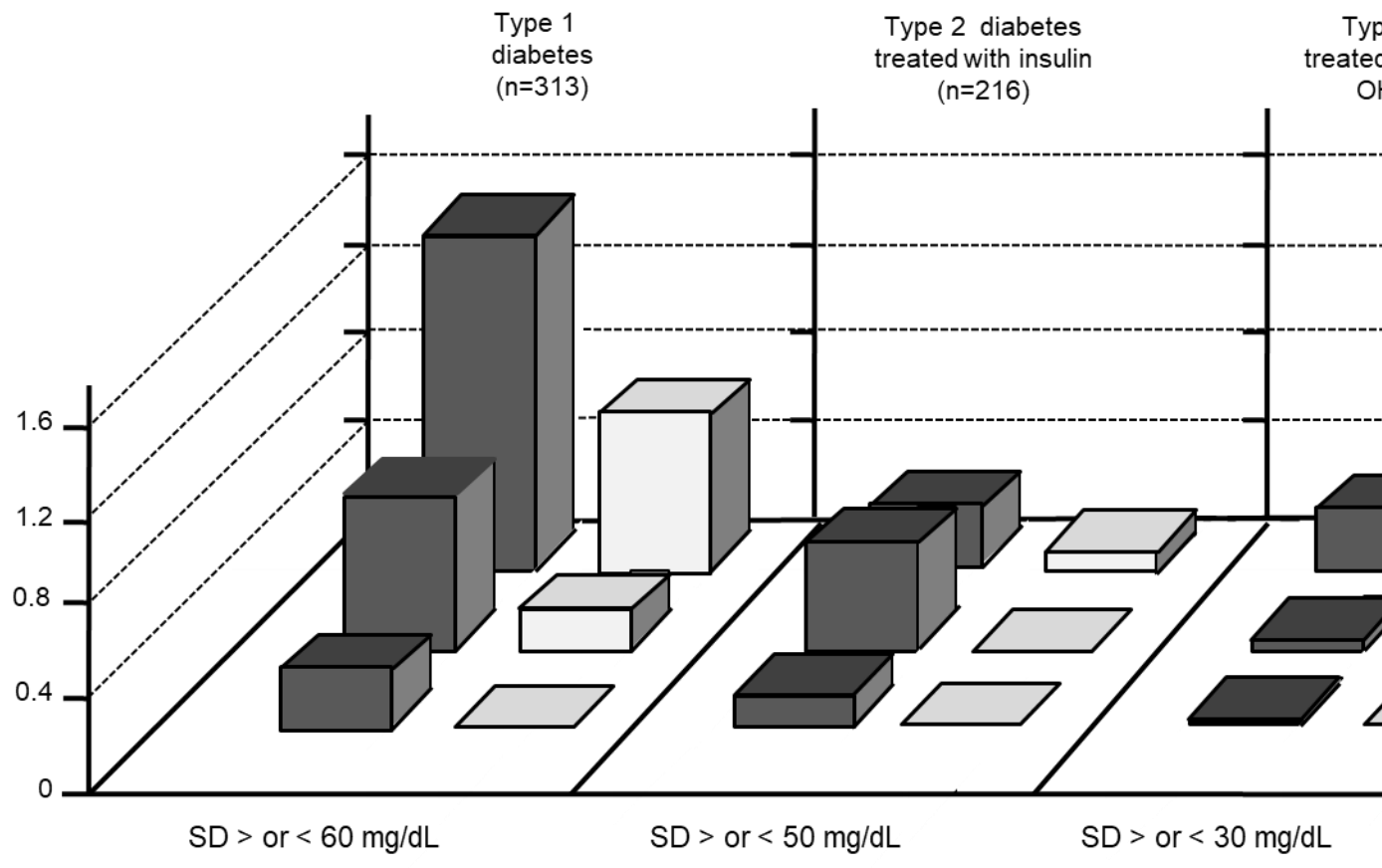
LBGI = Low Blood Glucose Index

HBGI = High Blood Glucose Index

MAG = Mean Absolute Glucose Variation

IQR = Interquartile Range, i.e. dispersion of data between the 25^{th} and 75^{th} percentile around the median

AGP = Averaged Glycemic Profile over several consecutive days (14 days with the Free Style Libre)


Type 1
diabetes
(n=313)
Type 2 diabetes
treated with insulin
(n=216)
1.6
1.2
0.8
0.4
0
SD > or < 60 mg/dL
SD > or < 50 mg/dL
SD > or < 30 mg/dL

Metrics	Computation	Interpretation	Adva
SD of glucose	From the mean square deviation (variance)	Short-term within-day glucose variability	Traditional measu data such as those directely calculate
CV for glucose	Calculated as %: [SD/mean glucose]x100	Short-term within-day glucose variability. A value of 36% separates stable from unstable diabetes [6, 26]	Adjusted on the m SD and mean by u
MAGE	Mean differences from peaks to nadirs	Short-term within-day glucose variability	Major glucose fluc devices but requir
MODD	24-h mean absolute differences between 2 values measured at the same time point	Short-term between-day glucose variability	Not directly given compu
CONGA	Integrates the duration and degree of glucose excursions	Short-term within-day temporal glucose variability	
ADRR	Sum of the daily peak risks for hypo- and hyperglycaemia	Composite of short-term wiithin- and between-day temporal glucose variability	
LBGI ; HBGI	Preceded by a log transform to render symetric the skewed distribution of glucose values	Risk indices for predicting hypo or hyperglycaemia, respectively	Complex calcul toward investig
MAG	Incremental/decremental changes in glucose	Short-term within-day temporal variability	Rela
IQR of AGP	Distribution of glucose data at a given time point by using non-parametric statistics	Reflects the presence/absence of day-to-day synchrony in glucose patterns at a given time	Measure of dispe those recorded at Directly given by t
Visit-to-visit changes	Measures of variability (SD,CV…) of HbA_{1c} ,FPG… between sequential visits	Long-term variability in glucose homeostasis	Measures that are