Glycaemic variability in diabetes: clinical and therapeutic implications

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Glycaemic variability is an integral component of glucose homoeostasis. Although it has not yet been definitively confirmed as an independent risk factor for diabetes complications, glycaemic variability can represent the presence of excess glycaemic excursions and, consequently, the risk of hyperglycaemia or hypoglycaemia. Glycaemic variability is currently defined by a large and increasing number of metrics, representing either short-term (within-day and between-day variability) or long-term glycaemic variability, which is usually based on serial measurements of HbA_{1c} or other measures of glycaemia over a longer period of time. In this Review, we discuss recent evidence examining the association between glycaemic variability and diabetes-related complications, as well as non-pharmacological and pharmacological strategies currently available to address this challenging aspect of diabetes management.

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Introduction

Strategies for the management of glycaemia in patients with diabetes should aim to address the three main components of dysglycaemia: chronic hyperglycaemia, hypoglycaemia, and glycaemic variability.[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 shown the association between prolonged poor glycaemic control and the development of microvascular and, to a lesser extent, macrovascular complications.[3,4] During the past decade, deleterious effects of both short-term glycaemic variability (within-day glucose fluctuations; peaks to nadirs), and long-term variations, as measured by changes in fasting plasma glucose (FPG) and HbA_{1c}, have been proposed,[5,6] although definitive evidence on hard clinical outcomes remains scarce.[7]

Notably, the availability of glucose monitoring, especially continuous glucose monitoring (CGM) has become of considerable value in informing management decisions, whereas HbA_{1c} used in isolation can be misleading.[8] Short-term glycaemic variability is of increasing concern to health-care professionals intent on preventing excessive glucose fluctuations, posing the potential risk of precipitating episodes of hyperglycaemia or hypoglycaemia,[6] negatively affecting patients' quality of life.[9] Short-term and longer-term glycaemic variability also seem to be associated with increased episodes of severe hypoglycaemia, which in turn are associated with adverse cardiovascular outcomes and all-cause mortality.[10,11] However, definitive evidence for the role of glycaemic variability in the genesis and severity of adverse clinical outcomes in people with diabetes is scarce compared with the evidence for the negative effects of chronic glucose exposure, as assessed by HbA_{1c}.[2–4]

In this Review, we assess the emerging evidence on the clinical and therapeutic relevance of glycaemic variability in diabetes, focusing on studies published in the past few years while also drawing on landmark earlier studies. The clinical association between glycaemic variability and diabetes complications is difficult to establish because of heterogeneity between studies, including their design and, notably, the different metrics used to assess glycaemic variability. Additionally, most antidiabetes treatments affect components of the so-called glycaemic triumvirate (ambient hyperglycaemia, glycaemic variability, and hypoglycaemia) to different degrees.[1,12–16] Individualising care on the basis of change in CGM and glycaemic variability could be an important aspect of precision medicine in diabetes, although such an objective might take a long time to achieve.

Metrics of glycaemic variability: does profusion create confusion?

Glycaemic variability is usually defined by the measurement of fluctuations of glucose or other related parameters of glucose homoeostasis over a given interval of time. This description covers two predominant categories of measurements (table): short-term glycaemic variability, represented by both within-day and between-day glycaemic variability, and long-term glycaemic variability, based on serial determinations over a longer period of time, usually involving HbA_{1c}, but sometimes serial FPG and postprandial glucose (PPG) measurements. However, the acceptance and clinical relevance of this proposed classification remains subject to debate. For many years, short-term glycaemic variability was calculated from self-monitoring of blood glucose (SMBG) measurements,[7] but this method has been progressively replaced over the past few years by CGM.[17,18] SMBG, at best, provides an abbreviated diurnal blood glucose profile,[19] whereas CGM, with interstitial glucose measurements at 5 min intervals, provides a more comprehensive record, covering both day and night, and is regarded as the gold standard method for assessment of short-term glycaemic variability.[17,18] Fleisher and colleagues[19] also reported a poor correlation (R^2=0·26, p<0·05) between the mean amplitude of glycaemic excursion (MAGE) obtained from structured SMBG testing and MAGE computed from CGM. However, structured SMBG can be used to determine the two main components of short-term glycaemic variability—ie, the within-day and between-day glycaemic variability. Traditional measures

	Computation	Interpretation	Advantages and limitations
SD of mean glucose concentration	From the mean SD (variance)	Short-term within-day glucose variability	Traditional measure of dispersion for large quantities of data such as those recorded with CGM systems and directly calculated by devices
CV for glucose	Calculated as %: (SD ÷ mean glucose) ×100	Short-term within-day glucose variability in diabetes	Adjusted on the mean glucose concentration and easily calculated from SD and mean
MAGE	Mean differences from peaks to nadirs	Short-term within-day glucose variability	Major glucose fluctuations; not directly reported by CGM devices but is simple to calculate
MODD	24 h mean absolute differences between two values measured at the same timepoint	Short-term between-day glucose variability	Not directly reported by CGM devices; requires additional computation, but is easy to interpret
CONGA	Integrates the duration and degree of glucose excursions	Short-term within-day temporal glucose variability	Complex calculation
ADRR	Sum of the daily peak risks for hypoglycaemia and hyperglycaemia	Composite of short-term within-day and between-day temporal glucose variability	Complex calculation
LBGI and HBGI	Preceded by a log transformation to render symmetrical the skewed distribution of glucose values	Risk indices for predicting hypoglycaemia (LBGI) or hyperglycaemia (HGBI)	Complex calculation; more oriented towards capturing the risk for severe hypoglycaemia and hyperglycaemia than assessing glycaemic variability
MAG	Incremental or decremental changes in glucose	Short-term within-day temporal variability	Fairly complex calculation
IQR of AGP	Distribution of glucose data at a given timepoint calculated from non-parametric statistics	Reflects the presence or absence of day-to-day synchrony in glucose patterns at a given time	Measure of dispersion for small amount of data such as those recorded at a given timepoint over several days (directly reported by the Abbott FreeStyle Libre)
Visit-to-visit changes	Measures of variability (SD, CV) of HbA_{1c}, FPG, etc between sequential visits	Long-term variability in glucose homoeostasis	Measures that are very heterogeneous in design

CGM=continuous glucose monitoring. CV=coefficient of variation. MAGE=mean amplitude of glycaemic excursions. MODD=mean of daily differences. CONGA=continuous overlapping net glycaemic action. ADRR=average daily risk range. LBGI=low blood glucose index. HBGI=high blood glucose index. MAG=mean absolute glucose variation. AGP=averaged glycaemic profile over several consecutive days (14 days with the Abbott FreeStyle Libre). FPG=fasting plasma glucose.

Table: **Main metrics for assessment of glycaemic variability**

of within-day glycaemic variability can include the SD or derived coefficient of variation (CV), or both. When averaging each daily SD or CV, the mean of within-day daily glycaemic variability over the stated time period can also be estimated.[20] Another method is to calculate the SD from the averaged glucose profiles, which is referred to as the daily SD by average. The estimate of daily SD by average is usually smaller than the mean of within-day daily SD; this underestimation can be exaggerated when the between-day glucose patterns become more varied. A large disparity between the two indices reflects a high degree of between-day glycaemic variability.[21]

The metric considered to be the best for estimating the between-day glycaemic variability is the mean of daily differences (MODD),[21] which was introduced in the early 1970s by Molnar and colleagues.[22] The computation is based on calculation of the absolute difference between two glucose values measured at the same time within a 24 h interval—a high MODD score is indicative of a large between-day glycaemic variability. This metric cannot be determined with available CGM devices and thus requires additional computation.

Another glycaemic variability parameter is the spread of glucose data at given timepoints over several consecutive days. This parameter is used by the flash glucose monitoring system FreeStyle Libre (Abbott, Abbott Park, IL, USA), which computes the averaged glycaemic profile over a defined period of 14 days and reports the results as IQRs.[23] A high IQR indicates a loss of synchrony of between-day glucose patterns—ie, a high between-day glycaemic variability—whereas a low IQR implies low between-day glycaemic variability.[20,21] Other more complex metrics are also available for assessment of short-term glycaemic variability, but are rarely applied in routine clinical practice (table).

Although we have mainly focused on the metrics of glycaemic variability that are based on the SD, while omitting discussion of the more complicated computations, measurement values can remain difficult to interpret. Therefore, simplifying the message is a prerequisite for health-care providers to be able to easily calculate and interpret short-term glycaemic variability. We previously proposed that the CV is the most appropriate index for assessing mean within-day daily glycaemic variability, independent of the mean glucose concentration, with a cutoff threshold value of 36% to separate 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 by use of the grading system developed by the American Diabetes Association), it was adopted in the 2017 Advanced Technologies & Treatments for Diabetes Congress (ATTD) International Consensus on the Use of Continuous Glucose Monitoring.[18] In 2005, based on

personal observations, a threshold value equivalent to a CV of 33% was suggested by Hirsch[24] as an ideal target derived by multiplying the SD by three and dividing by the mean glucose concentration. Some experts have expressed concern about the difficulty of defining a meaningful threshold for short-term glycaemic variability to differentiate labile from stable diabetes. However, similar difficulties were encountered in determining clear recommendations for HbA_{1c} that separate satisfactory from unsatisfactory control of diabetes and in reaching a definition of hypoglycaemia.[25] As described in our previous publication,[6] we chose to consider a group of individuals treated with dietary measures with or without insulin sensitisers and with a minimal risk of hypoglycaemia as a reference for stable diabetes, 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 glycaemic variability, namely long-term glycaemic variability, is usually based on visit-to-visit measurements of HbA_{1c}, FPG, or PPG,[26] with the subsequent calculation of their SD and CV. Long-term glycaemic variability is partly a reflection of ambient hyperglycaemia because measures of long-term variability correlate with either mean concentration of blood glucose (r=0·73)[7] or mean HbA_{1c} (r=0·55).[27] This definition of long-term variability is likely to be a generic term that encompasses different concepts and definitions.[28]

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

Glucose variability and clinical outcomes in people with and without diabetes

Before 2015, several studies had shown a positive association between glycaemic variability and diabetes complications, both macrovascular and microvascular.[29] Since 2015, new evidence has also emerged in support of glycaemic variability as an independent risk factor for total mortality and death due to cardiovascular disease in both type 1 and type 2 diabetes.[26,30–34]

Glycaemic variability increased recurrent cardiovascular events and mortality in people with diabetes following episodes of acute ischemic stroke.[35] An elevated glycaemic variability was significantly associated with the 3 month cardiovascular composite outcome, with increased cardiovascular outcomes in the highest glycaemic variability quartile, similar in both normoglycaemic and hyperglycaemic groups. Moreover, in a 2018 study, a strong association was shown between long-term glycaemic variability and mortality in patients aged 70 years and older with diabetes.[36] Notably, within-day glycaemic variability evaluated by CGM was associated with 10 year cardiovascular risk in patients with well controlled diabetes based on HbA_{1c}.[37] These data are consistent with evidence that indicates short-term glycaemic variability might adversely affect plaque stability in individuals with or without diabetes,[38] is associated with subclinical coronary atherosclerosis,[39] and extends corrected QT interval duration and dispersion.[40] Long-term HbA_{1c} variability has been associated with an increased risk of developing atrial fibrillation[41] and incidence of heart failure.[42] Moreover, reducing glycaemic variability with insulin via continuous subcutaneous infusion is accompanied by an increase in circulating endothelial progenitor cells in patients with type 1 diabetes.[43] Long-term glycaemic variability (HbA_{1c}) in type 2 diabetes has been associated with the risk of developing diabetic nephropathy.[44,45] An association between long-term glycaemic variability (HbA_{1c}) in patients with type 1 diabetes and diabetic retinopathy has also been reported in some studies.[46,47] Glycaemic variability also causes inner retinal sensory neuropathy in patients with type 1 diabetes.[48] However, no association was seen between short-term or long-term glycaemic variability and the progression of microvascular outcomes in type 1 diabetes in the Diabetes Control and Complications Trial (DCCT).[7]

Glycaemic variability seems to be a risk factor for diabetic neuropathy in people with type 2 diabetes, not only in terms of retinal neurodegeneration,[46] but also in terms of polyneuropathy and cardiovascular autonomic neuropathy.[49,50] A reduced cardiac autonomic modulation is evident in women with type 2 diabetes and high glycaemic variability.[51]

There is considerable interest in the emerging association between glycaemic variability and decline in cognitive function.[52,53] HbA_{1c} variability seems to predict symptoms of depression in individuals with a mean age of 72·74 years (SD 4·63 years) with type 2 diabetes,[54] including the risk of developing Alzheimer's disease.[55] Repetitive glycaemic variability in the brain has also been suggested to possibly produce relative cerebral hypoglycaemia,[56] 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.

Although cumulative evidence suggests a role for glycaemic variability in diabetes complications, some studies have had contradictory findings. Investigators of a post-hoc analysis from the DCCT[7] assessed the association of glycaemic variability within and between quarterly seven-point glucose profiles with the development and progression of retinopathy, nephropathy, and cardiovascular autonomic neuropathy. Measures of variability included the within-day and updated mean (over time) of the SD and MAGE, and the longitudinal within-day, between-day, and total variances. No measure of within-day variability was associated with any adverse outcome, when adjusted for mean blood glucose concentration.[7] In an earlier analysis of the DCCT in which

glycaemic variability was evaluated as a risk factor for diabetes complications, the results were predominantly negative, but also inconsistent, with HbA_{1c} variability associated with increased risk of retinopathy.[57,58] Limitations of this study include a reliance on seven-point SMBG profiles at quarterly intervals to represent the mean blood glucose concentrations and variability over time.[58] Such infrequent measurements might lead to erroneous measures of glycaemic variability.[58]

Notably, glycaemic variability also seems to have an effect in people without diabetes. It is has been reported as a risk factor for a worse outcome in several acute conditions,[59] although, when corrected for other confounding variables, this association can be lost.[60] However, findings from one study suggested that glycaemic variability remains a risk factor for longer hospitalisation and increased short-term and long-term mortality in diabetic and non-diabetic patients, even when correcting for several confounding variables, including severity of illness, average blood glucose concentration, blood glucose measurement frequency, and having at least one severe hypoglycaemia event (<2·22 mmol/L, or <40 mg/dL, blood glucose concentration).[61] Glycaemic variability also seems to be associated with an increased risk of a major cardiovascular event in the 30 days following acute coronary syndrome,[62] isolated cardiac valvular surgery,[63] and intracerebral haemorrhage.[64] It has also been associated with an increased risk of mortality in the general population.[65] Visit-to-visit variability of FPG, defined as the coefficient of variation of three values of FPG measured in examination periods, is strongly associated with mortality in individuals without diabetes in the intensive care unit, but less so in patients with diabetes.[66] Similarly, a poorer 30 day functional outcome following acute intracerebral haemorrhage was reported in those individuals without diabetes and increased glycaemic variability than in those with little glycaemic variability.[64]

Among people with diabetes in intensive care, increasing glycaemic variability was not associated with increased mortality among patients with an HbA_{1c} of more than 8·5% (or 69 mmol/mol).[67] Hypoglycaemia was associated with mortality, but previous exposure to hyperglycaemia had a lesser effect on this association. Previous exposure to hyperglycaemia might act as a preconditioning factor, minimising the effect of glycaemic variability.

Intervention studies

Importantly, long-term intervention studies will be necessary to provide compelling evidence for a beneficial effect of reducing short-term glycaemic variability on hard outcomes, such as the development and progression of microvascular and macrovascular diseases. In all studies aimed at attenuating the magnitude of glycaemic variability or of postprandial excursions reported so far, the tested group and its comparator group received pharmacological interventions with different treatment regimens, but always with at least one insulin preparation in both groups. For example, the HEART2D Study,[68] was initially designed to answer whether control of basal or prandial hyperglycaemia was best for reduction of cardiovascular outcomes in patients with poorly controlled type 2 diabetes. Patients were assigned to either a basal insulin strategy or an insulin regimen with three daily injections of rapid insulin-acting analogues before meals. At the end of the study, a similar lowering effect on ambient hyperglycaemia was reported with the two insulin regimens. A modest and less than expected reduction in postprandial excursions was achieved with prandial insulin compared with basal insulin. The small differences might explain why this study could not provide conclusive results in terms of cardiovascular outcomes when the two insulin regimens were compared.[68] However, in a post-hoc analysis, a beneficial effect on reducing PPG was reported in individuals older than 65·7 years of age and those with a longer diabetes duration.[69]

The same remark can be applied to the FLAT-SUGAR study,[13] which was designed to test whether an add-on therapy with exenatide to an ongoing basal insulin regimen can reduce short-term glycaemic variability and improve markers of cardiometabolic risk in patients with insulin-requiring type 2 diabetes and high cardiovascular risk. Albuminuria, serum C-reactive protein, serum interleukin 6, and urinary prostaglandin $F_{2\alpha}$ were similar for the two treatment strategies. Group mean change of CV from baseline differed by only 2·87% (p=0·047) when patients who received an add-on therapy with exenatide were compared with those who did not. This raises the question as to whether such a small difference can affect the markers of cardiometabolic risk. In addition, the duration of the study was very short, and both groups were treated with insulin. Insulin has an inhibitory action on inflammation, thrombosis, and activation of oxidative stress,[70] so the potential benefit of reducing glycaemic variability or postprandial excursions might not be apparent because of the predominant response to insulin. Another difficulty lies in the fact that most antidiabetes therapies exert their effects on blood sugar control via a concomitant reduction in both ambient hyperglycaemia and glycaemic variability.[13] The ideal randomised intervention trial for testing the specific effect of reducing glycaemic variability on cardiometabolic risk markers (and on clinical cardiovascular outcomes) should avoid the use of insulin treatment in the comparator groups[71] and aim to achieve a similar degree of ambient hyperglycaemia in those individuals with or without improvement in glycaemic variability. Another important challenge for long-term intervention studies for reducing glycaemic variability is the difficulty in ensuring that participants can use CGM over a

prolonged period of time, unless suitable wearable devices become available. As such, whether such trials are technically, financially, and ethically feasible is questionable. For all these reasons, in-vitro experiments on cells or in-vivo experimental studies in animals and human beings therefore currently provide the best opportunity for investigating the potential deleterious role of abnormally high glycaemic variability, despite the many obvious limitations of such data.

Glycaemic variability and tissue damage

Findings from two in-vitro studies done almost 20 years ago (the first showing a specific damaging effect of glycaemic variability) showed that short-term (4 days) and long-term (21 days) glucose oscillation enhanced human tubule-interstitial cell growth and collagen synthesis[72] and accelerated apoptosis in human umbilical vein endothelial cells[73] more than exposure to a constantly high glucose concentration. Shortly afterwards, oxidative stress was shown to be the key player in producing damage to endothelial cells.[74] Several other studies have since confirmed that oscillating glucose concentrations, via oxidative stress, can adversely affect the cells of different organs.[29] More recently, the source and targets of oxidative stress during glucose fluctuation have been further characterised. The mitochondrion is still considered the key component in inducing superoxide production during glycaemic variability, together with NADPH oxidase.[75,76] The involvement of the AKT pathway in this process has also been recognised.[77] Blood glucose fluctuation accelerates renal injury, which involves inhibition of the AKT signalling pathway in diabetic rats.[78] Glycaemic variability can also induce increased chromatin remodelling,[79] which can have an important role in glycaemic variability-induced metabolic memory.[80]

Studies in human beings are less consistent. Some have shown that oxidative stress is produced during glycaemic variability[1,81] and that oscillating glucose is more deleterious to endothelial function via oxidative stress than mean glucose concentration in individuals with or without type 2 diabetes.[82] However, other studies did not confirm that short-term glycaemic variability was associated with raised oxidative stress markers in healthy volunteers[83,84] and in people with type 1 diabetes.[84] Because insulin has an inhibitory action on inflammation, thrombosis, and activation of oxidative stress, the possibility that insulin affected the results, positively or negatively, cannot be excluded. Notably, an increased glycaemic variability accompanied by an increase in oxidative stress has been reported in patients with type 2 diabetes in remission after bariatric surgery.[85] Evidence also exists that hyperglycaemia after recovery from hypoglycaemia leads to worsening endothelial function and increasing oxidative stress and inflammation both in healthy control individuals and patients with type 1 diabetes, but not when recovery from hypoglycaemia is followed by normoglycaemia.[86]

Glycaemic variability and hypoglycaemia

Achievement of near normoglycaemia is a key objective in the management of diabetes. This objective is well supported by observational, epidemiological, and interventional studies confirming the association between hyperglycaemia and cardiovascular events, premature death, and microvascular complications.[87]

Unfortunately, the maintenance of normoglycaemia over a lifetime of diabetes, while also attempting to avoid hypoglycaemia, is a major challenge for patients.[88] In 2000, the investigators of the ACCORD study[89] showed that trying to achieve a glycaemic goal that was too stringent (HbA_{1c} <6%, 42 mmol/mol) with intensive therapy resulted in increased frequency of hypoglycaemia, although this increase was not causally related to an increased risk of cardiac death. In clinical practice, the principle should be to achieve the best glycaemic control possible, while limiting the risk of hypoglycaemia. Such a strategy will, however, increase the risk of microangiopathic complications, especially when applied to younger patients with a long life expectancy. Clinicians should also be aware that excessive short-term glycaemic variability, even in the presence of target HbA_{1c} levels, can contribute to the risk of hypoglycaemia. This risk is increased when the mean blood glucose concentration is low or if deviations around the mean glucose concentrations are large,[90] suggesting the need to reduce short-term glycaemic variability. The role of acute glucose fluctuations as a risk factor for hypoglycaemia has only been fully shown with CGM technology. In a study in patients with type 2 diabetes who were being treated with oral antidiabetes drugs, insulin, or both, mean glucose concentration and its SD were the best variables for predicting the frequency of asymptomatic hypoglycaemia.[91] Incident asymptomatic hypoglycaemia (interstitial glucose value <3·1 mmol/L or <56 mg/dL) was negatively associated with mean glucose concentration, and positively associated with short-term glycaemic variability, as represented by the SD.[91] Similar findings were reported in an analysis if 828 day-patient glycaemic profiles (ambulatory CGM) in patients with type 1 diabetes, type 2 diabetes treated with insulin, and non-insulin-treated type 2 diabetes (figure).[92] The three groups were further divided into three subgroups on the basis of 24 h mean glucose values (<8·3 mmol/L [<150 mg/dL], 8·3–10·0 mmol/L [150–180 mg/dL] or >10 mmol/L [>180 mg/dL]). In each subset, the frequency of hypoglycaemic episodes (interstitial glucose values <3·1 mmol/L or <56 mg/dL) was compared according to whether the within-day glycaemic variability (SD around the mean glucose value) was above or below the mean SD in each selected subgroup, which was 60 mg/dL (3·3 mmol/L) for type 1 diabetes, 50 mg/dL (2·8 mmol/L) for insulin-treated type 2 diabetes, and 30 mg/dL (1·7 mmol/L) for patients with type 2 diabetes not treated with insulin (figure). The

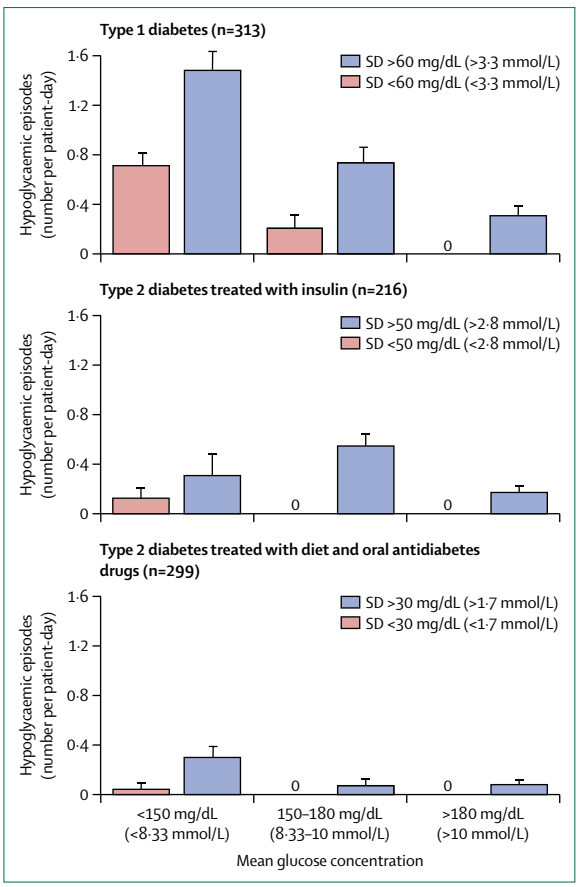

Figure: **Hypoglycaemic episodes in patients with diabetes**
Total (symptomatic and asymptomatic) hypoglycaemic episodes (interstitial glucose concentration <56 mg/dL [<3·1 mmol/L]) during continuous glucose monitoring expressed as number per patient-day in a study of patients with type 1 diabetes, type 2 diabetes treated with insulin, and type 2 diabetes treated with diet and oral antidiabetic drugs. Each group was further submitted to a stepwise stratification by mean glucose concentration and then by glycaemic variability expressed as SD around the mean glucose concentation. Data in columns are means plus SE. Figure is adapted from Monnier et al,[92] by permission of Springer US.

frequency of hypoglycaemic episodes when ranked according to decreasing ordinal were type 1 diabetes, then insulin-treated type 2 diabetes, and then non-insulin-treated type 2 diabetes; within each category of diabetes, the frequency of hypoglycaemic episodes increased with decreasing mean glucose values. In each subgroup, the frequency of hypoglycaemic episodes increased significantly when the glycaemic variability exceeded the mean SD value, representing an increased risk for hypoglycaemia. In a similar mixed population of people with diabetes in another study, the incidence of hypoglycaemic events was three to six times greater in patients with a within-day CV of more than 36% (referred to as labile diabetes) than in a subgroup with a CV of 36% or less (considered to be stable), irrespective of the type of diabetes or treatment with oral diabetes drugs or insulin.[6] The mean glucose concentrations were similar across the subgroups in the study (type 1 diabetes, type 2 diabetes treated with oral drugs [including sulfonylureas], and type 2 diabetes treated with insulin), confirming that the within-day glycaemic variability has an important role with respect to the incidence of hypoglycaemia.

Therapeutic implications

There are several possibile methods for reducing glycaemic variability in clinical practice, using pharmacological and non-pharmacological tools.

Non-pharmacological options

Findings from the HypoCOMPaSS trial suggested that training in the avoidance of low blood glucose concentrations for adult patients with type 1 diabetes who have frequent severe hypoglycaemia and impaired awareness of hypoglycaemia could decrease glycaemic variability.[93] Additionally, in people with type 2 diabetes or impaired glucose tolerance, moderate physical exercise has been shown to lower glycaemic variability and reduce oxidative stress.[94] Combining CGM with appropriate education seems to be a promising strategy for improving glycaemic control and glycaemic variability.[16] In the DIAMOND trial,[16] compared with usual care, the use of CGM in patients with type 1 diabetes resulted in an improvement in both HbA_{1c} (–0·6%) and glycaemic variability (CV –4%) from a similar baseline value of 42%. In a 2017 review, Rodbard[95] reported that CGM has beneficial effects on metabolic control (reduced risk of hypoglycaemia and hyperglycaemia; decreased glycaemic variability, mean glucose concentration, and HbA_{1c} values) in both type 1 and type 2 diabetes and across various insulin treatment regimens (either multiple daily injections or continuous subcutaneous insulin infusion).[95]

Pharmacological options

Using glucose-lowering drugs to achieve a normal or near-normal HbA_{1c} without increasing the risk of hypoglycaemia is crucial for the correct management of diabetes, especially during the early stages of type 2 diabetes when dysglycaemia is limited to an exaggerated dawn phenomenon or abnormal postprandial excursions.[96] A post-hoc analysis of the OPTIMA study, in which CGM profiles were assessed in patients with type 2 diabetes receiving the dipeptidyl peptidase-4 (DPP-4) inhibitor drugs sitagliptin or vildagliptin (as add-on therapies to metformin), showed that DPP-4 inhibitors achieved a reduction of glycaemic variability.[96] Similar effects have also been reported with the sodium-glucose co-transporter-2 (SGLT2) inhibitors in patients with type 1 diabetes.[97,98]

When oral antidiabetes drugs fail to achieve or maintain satisfactory glycaemic control in patients with type 2 diabetes, it is often necessary to introduce injectable therapies, such as a basal insulin or a glucagon-like peptide-1 (GLP-1) receptor agonist.[99] In a randomised trial, the addition of exenatide once weekly to metformin in patients with type 2 diabetes improved

glucose control, with a significant decrease in FPG, 2 h PPG, and glycaemic variability, and increased the time spent in normoglycaemia, while reducing time spend in hypoglycaemia.[100] Similarly, in a pooled trial analysis,[101] addition of lixisenatide to basal insulin therapy significantly decreased the risk of hypoglycaemia and glycaemic variability. When insulin glargine 100 U/ml was compared with insulin glargine 300 U/ml in a randomised crossover trial in patients with type 2 diabetes, short-term glycaemic variability did not differ between treatments, except for the MODD being lower with 300 U/ml than with 100 U/ml.[102]

In the DEVOTE trial,[12] the cardiovascular safety of insulin degludec was compared with insulin glargine 100 U/ml in patients with type 2 diabetes at high cardiovascular risk. The treatments led to similar glycaemic control (HbA_{1c}) and degludec was non-inferior to glargine with respect to the primary cardiovascular outcome. Notably, insulin degludec lowered episodes of confirmed severe hypoglycaemia by 40% and nocturnal severe hypoglycaemia by 53%. In a post-hoc analysis of this trial (DEVOTE 2),[10] higher inter-day FPG variability was associated with increased risks of severe hypoglycaemia and all-cause mortality.

When basal insulin supplementation is deemed insufficient in type 2 diabetes, two further options are available: the addition of a GLP-1 receptor agonist or a short-acting insulin analogue. There are two randomised studies, the FLAT-SUGAR trial[13] and the AWARD-4 substudy,[14] that have assessed the effect of basal insulin in combination with a GLP-1 receptor agonist on both ambient hyperglycaemia and glycaemic variability. The FLAT-SUGAR trial was a 26 week randomised trial comparing a basal-bolus insulin regimen with basal insulin and the short-acting GLP-1 receptor agonist exenatide, injected twice daily before the largest meals. This therapeutic strategy resulted in a reduced short-term glycaemic variability, although improvement in HbA_{1c} was similar in both therapeutic groups.

In the AWARD-4 substudy,[14] which was done over an initial period of 26 weeks and extended to 52 weeks, between-day glycaemic variability was slightly but significantly decreased with the once-weekly GLP-1 receptor agonist dulaglutide plus prandial insulin lispro, when compared with a basal-bolus insulin regimen of insulin glargine U100 plus prandial lispro. However, the results should be interpreted with caution, because whether the subgroups were identified before or after randomisation of the overall population of the AWARD-4 main trial is not clear.[103] However, improvements in ambient hyperglycaemia (percentage of participants within a glucose target range of 3·9–9·0 mmol/L), glycaemic variability, and risk of hypoglycaemia have been reported when a fixed-ratio combination of basal insulin degludec and the GLP-1 receptor agonist liraglutide was compared with either drug alone.[104]

Search strategy and selection criteria

We searched PubMed for articles published in English from database inception up to Jan 31, 2018, using the search terms "glycaemic variability", "glucose variability", "fasting glucose variability", "HbA_{1c} variability", "glucose fluctuation", and "oscillating glucose". We reviewed and selected retrieved references on the basis of relevance. We gave priority for inclusion to relevant scientific literature published from 2015 onwards, although selected key older references are also cited.

In summary, management of type 2 diabetes using incretin modulators (DPP-4 inhibitors) at an early stage of the disease, or incretin mimetics (GLP-1 receptor agonists) at a later stage, can reduce ambient hyperglycaemia and glycaemic variability without increasing the risk of hypoglycaemia. The addition of ultra-long-acting insulins (eg, insulin degludec, glargine 300 U/ml) can also reduce glycaemic variability.[105]

Conclusions

Now that the improved availability of CGM has made blood glucose monitoring easier and more meaningful, glycaemic variability is emerging as an additional glycaemic target, even though doubt remains over whether both short-term or long-term glycaemic variability should be considered independent risk factors for diabetes-related complications. The potential risks associated with glycaemic variability seem likely to be related to possible vascular damage due to excessive glucose fluctuations and an increased risk of hypoglycaemia and its consequences. For glycaemic variability to be useful in clinical practice, indices need to be easily obtained and interpreted, and health-care providers must be aware of the possible lifestyle and therapeutic options available that might help to reduce glycaemic variability safely, without compromising glycaemic control. Restriction of the assessment of within-day glycaemic variability based on the magnitude of the SD and the derived CV should help to limit confusion. Future developments in CGM systems (and related technologies such as flash glucose monitoring) and indices for better defining and deciphering glycaemic control and glycaemic variability should help to improve understanding of the clinical relevance of glycaemic variability in the management of diabetes.

Contributors

All authors contributed equally to the literature search, interpretation, and writing of the Review. All authors approved the final submitted version.

Declaration of interests

We declare no competing interests.

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