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REVIEW ARTICLE

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Glycaemic variability: The under-recognized therapeutic target in type 1 diabetes care

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Abstract

Type 1 diabetes mellitus (T1DM) remains one of the most challenging long-term conditions to manage. Despite robust evidence to demonstrate that near normoglycaemia minimizes, but does not completely eliminate, the risk of complications, its achievement has proved almost impossible in a real-world setting. HbA1c to date has been used as the gold standard marker of glucose control and has been shown to reflect directly the risk of diabetes complications. However, it has been recognized that HbA1c is a crude marker of glucose control. Continuous glucose monitoring (CGM) provides the ability to measure and observe inter- and intraday glycaemic variability (GV), a more meaningful measure of glycaemic control, more relevant to daily living for those with T1DM. This paper reviews the relationship between GV and hypoglycaemia, and micro- and macrovascular complications. It also explores the impact on GV of CGM, insulin pumps, closed-loop technologies, and newer insulins and adjunctive therapies. Looking to the future, there is an argument that GV should become a key determinant of therapeutic success. Further studies are required to investigate the pathological and psychological benefits of reducing GV.

KEYWORDS
continuous glucose monitoring, glycaemic variability, type 1 diabetes mellitus

1 | INTRODUCTION

The management of, and outcomes for, individuals with type 1 diabetes mellitus (T1DM) is an ongoing, modern-day challenge for those living with the condition, healthcare professionals and healthcare systems. Despite an increasing understanding of the complex pathophysiology of T1DM, the management of this condition continues to be a precarious balance between the daily consequences of insulin treatment and the risk of longer-term complications.

The Diabetes Control and Complications Trial (DCCT) and subsequent Epidemiology of Diabetes Interventions and Complications (EDIC) studies have shown that improvement in glycaemic control to near-normal levels in people with T1DM can significantly reduce the incidence of microvascular complications and provide a more sustained, glycaemia-independent reduction in risk of complication. This has been termed "metabolic memory" or the "legacy effect", describing a persistent benefit of improved control, even in a situation in which, subsequently, glycaemic control deteriorates.[1,2] One of the major questions of these seminal trials was the degree to which these study results were transferable into routine clinical practice. The recent study by Simmons et al. suggested that the achievement of near normoglycaemia required a high level of glucose monitoring and dynamic adjustment of insulin therapy in highly engaged and well-educated individuals.[3]

TABLE 1 Summary of main points and recommendations for clinical practice

1. GV can be more readily assessed in clinical practice as a result of the increasing uptake of continuous and intermittently viewed glucose monitoring
2. SD, CoV, AGP and TIR are commonly used to assess GV in clinical practice
3. GV is a more clinically relevant marker of daily glucose control and hypoglycaemia risk than HbA1c
4. We recommend that clinicians interpret glucose data in the context of mean glucose, SD, CoV, AGP and TIR; in T1DM, these often provide more meaningful data to inform therapeutic decisions than HbA1c
5. Achieving widespread recognition of GV as a key metric of therapeutic success will require the following: • Improved access to CGM for individuals living with diabetes • Standardized reporting of GV across all product reporting systems • Further studies investigating the relationship between CGM-derived GV with short- and long-term health outcomes
6. Modern technologies (CGM, CSII, closed-loop) and adjunctive agents (metformin, SGLT2) provide exciting opportunities to explore the impact of GV as a primary outcome of interest

Abbreviations: AGP, ambulatory glucose profile; CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion; GV, glycaemic variability; iCGM, integrated continuous glucose monitoring; SD, standard deviation; SGLT2, sodium-glucose co-transporter 2; T1DM, type 1 diabetes mellitus; TIR, time in range.

The level of resource required to deliver and sustain near-normal glycaemia without unacceptable hypoglycaemia in patients with T1DM has proved to be a significant, and as yet unmet, challenge to healthcare systems around the world. All major organizations, including the American Diabetes Association (ADA), the European Association for the Study of Diabetes (EASD) and the National Institute for Health and Care Excellence (NICE), make specific recommendations for adults with T1DM. The ADA makes some modifications in line with clinical considerations, suggesting that, in adults, HbA1c below 7% (53 mmol/mol) is a reasonable target, although a target of 6.5% (48 mmol/mol) may be set for selected individuals who can tolerate therapy without hypoglycaemia.[4] No country in the world has achieved these targets for a meaningful proportion of individuals living with T1DM.

In the UK there are approximately 400 000 individuals with a diagnosis of T1DM.[5] The majority (70%) of individuals with T1DM have HbA1c values above 7.5% (58 mmol/mol), while 15% of the total population have values over 10% (86 mmol/mol).[6] The numbers who achieve the UK national target of HbA1c below 6.5% (48 mmol/mol) are less than 9%, and this has remained virtually unchanged over the past 5 years.[6] Similarly, data from the T1D Exchange Registry of US patients with T1DM demonstrate that little improvement has been seen in mean HbA1c from 2010/2012 to 2016/2018; the adjusted mean HbA1c was 7.8% (62 mmol/mol) during the period 2010-2012 and 8.4% (68 mmol/mol) during the period 2016-2018 ($P < 0.001$ adjusted for age, diabetes duration, self-monitoring of blood glucose [SMBG] and use of continuous glucose monitoring [CGM]), with only 21% of patients reaching the target HbA1c of less than 7% (53 mmol/mol).[7-9] Swedish and German data indicate slightly better achievement, with mean HbA1c between 7.6% (60 mmol/mol) and 8% (64 mmol/mol), but these results fail to reach internationally agreed targets.[10-12] For a significant proportion of individuals, clinically problematic hypoglycaemia remains a major barrier to achievement of these targets.[13] This means that the majority of individuals living with T1DM by virtue of increased HbA1c continue to be exposed to a clearly identified, unacceptable and potentially avoidable risk of life-changing diabetes complications.[14] The difficulty in achieving normal or near-normal HbA1c that people with T1DM experience may be a function of increased glycaemic variability (GV). A recent study demonstrated that, in individuals without diabetes, mean GV measured by coefficient of variation (CoV) during the day and during the night was 17% ± 3% and 13% ± 4%, respectively, with a median of 96% of time spent between 70 and 140 mg/dL (3.9-7.8 mmol/L).[15] Data concerning individuals with T1DM suggest that even those patients with so-called "good variability" demonstrate a CoV of approximately 37%, which is more than twice that of individuals without diabetes.[16]

In this review we will discuss the limitations of HbA1c measurements and the emergence of GV as a significant and clinically meaningful glycaemic metric (Table 1). Increasing access to CGM in the context of T1DM care has facilitated the ability of clinicians to visualize directly both within- and between-day GV in routine clinical practice as a measure of glycaemic control, and to determine the impact of current and emerging therapeutic agents on the level of GV.

2 | HBA1C: A CRUDE MARKER OF GLUCOSE CONTROL

Robust randomized controlled trial (RCT) data from the DCCT demonstrate that lower HbA1c values lead to reduced risk of microvascular disease. However, it has become increasingly apparent that HbA1c is a crude marker of glucose control, and its major role and value is that of a predictive marker of risk.[17] Individuals with T1DM rely on static capillary glucose monitoring or more dynamic CGM to make day-to-day decisions concerning their diabetes care. Although GV has been described using seven-point glucose profiles, the recent growth in CGM, providing detailed 24-hour glucose profiles, has emphasized the large fluctuations in glucose that contribute to the mean glycaemic profile.[18,19] The relationship between these self-measured glucose profiles and HbA1c can be confusing, and it is clinically recognized that different individuals with diabetes can achieve the same HbA1c value with markedly different glucose profiles, GV and hypoglycaemia risk, and they subsequently experience diabetes in different ways.[17] HbA1c can mask marked fluctuations in glucose that not only have a negative impact on quality of life (QoL), but can also limit the ability to achieve optimal glucose levels without unacceptable hypoglycaemia.

3 | DEFINITION OF GLYCAEMIC VARIABILITY

GV can be short term, referring to the peaks and troughs of glucose within a day or between days, or can be longer term, referring to variability within markers of long-term control such as HbA1c. Different measures may be better suited to determining variability over different

durations. Some assessments are more effective at measuring intraday GV, such as standard deviation (SD), the CoV (SD divided by the mean) and, more recently, time in range (TIR), while others take into account the spread of glucose data over consecutive days, such as the ambulatory glucose profile, which reports results from a 14-day period in interquartile ranges. A high interquartile range reflects high interday GV. For the purposes of this review, CoV and SD measures were selected.

Rodbard et al. investigated the relationship between measures of glucose control and GV using an extensive array of measures in 81 adults with diabetes (T1DM, n = 64) during 1 week of blinded CGM. They defined four categories of variability: excellent (CoV under 33.5%); good (CoV between 33.5% and 36.8%); fair (CoV between 36.8% and 40.6%) and poor (CoV above 40.6%). They noted a curvilinear relationship between HbA1c and the CoV; those with a CoV under 25% had a negligible risk of hypoglycaemia.[20] An international consensus of expert opinion concluded that the CoV should become the primary measure of GV, with SD as a key secondary measure.[21] Stable glucose levels were defined as a CoV under 36%, and unstable glucose levels were defined as a CoV of at least 36%.[16] This provides a metric against which glucose data can be assessed and clinical intervention can be judged. The CoV could be a meaningful alternative to HbA1c or an additional metric in assessing "glycaemic effectiveness".

Rodbard et al. also recommended the use of TIR (time spent between 3.9 and 10.0 mmol/L) as a useful metric.[21] Indeed, over the past year TIR has become an attractive metric in both clinical and academic fields as it combines mean glucose and a measure of variability into a single measure. A recent consensus statement outlined target TIR values and time-below-range values in different conditions such as pregnancy and T1DM.[22] A recent re-analysis of seven-point capillary glucose profiles from the DCCT validated TIR as a marker of microvascular risk and showed that, for every 10% reduction in TIR, there was a 64% increase in risk of retinopathy and a 40% increase in risk of microalbuminuria.[23] In addition, among a population of 3262 patients with diabetes, an association of TIR and GV with development of diabetic retinopathy (DR) was shown in type 2 diabetes mellitus (T2DM).[24] The authors observed an HbA1c-independent association of TIR, assessed by CGM, with the prevalence of all stages of DR. In addition, the values indicating GV were significantly higher in patients with more advanced DR. Further adjustment of SD, but not the CoV or mean amplitude for glycaemic excursions (MAGE), attenuated the association of TIR, as a continuous variable, with mild non-proliferative retinopathy and vision-threatening retinopathy. The link between vision-threatening retinopathy and TIR, as a categorical variable, did not reach statistical significance after controlling for SD and the CoV, but did after controlling for MAGE.[24] When these GV metrics were considered, the relationship between TIR and the presence of any DR remained, suggesting a GV-independent effect of TIR on DR.

4 | GLYCAEMIC VARIABILITY AND RISK OF HYPOGLYCAEMIA

The relationship among intensive insulin therapy, tight glycaemic control (low HbA1c) and increased risk of hypoglycaemia was clearly demonstrated in the DCCT. Although the intensively controlled group experienced three times as many severe hypoglycaemia events than the conventionally treated group, the DCCT was a treat-to-target study with very tight pre-meal targets during an era in which non-analogue insulins were used. Although the DCCT and subsequent EDIC studies found that the risk of severe hypoglycaemia was related to HbA1c, other more recent population-based data, concerning patients who were using newer insulin delivery systems and analogue insulins, did not find this relationship. For example, observational data from the T1D Exchange study show that HbA1c levels were similar in those with and those without severe hypoglycaemia.[25] There is, however, a relationship between GV and risk of hypoglycaemia,[26] and between reduction in mean glucose and increase in the SD preceding episodes of severe hypoglycaemia, which allows prediction of more than 70% of severe hypoglycaemia events.[19]

5 | GLYCAEMIC VARIABILITY AND MICROVASCULAR OUTCOMES

GV has been associated with a number of markers of vascular complications, independent of average glucose control. For example, GV has been associated with retinal thickening and neurodegenerative defects in the retina that were independent of HbA1c.[27,28] It has also been associated with markers of autonomic cardiovascular (CV) function such as heart rate variability, particularly during the night.[29,30] More recently, CGM-defined GV has been associated with the presence of CV autonomic neuropathy.[31] GV strongly correlates with excitability markers of altered motor and sensory axonal function, but acute glucose levels (6-12 mmol/L) do not.[32] As such, GV may contribute to the development of CV autonomic dysfunction in adults with T1DM. Experimental data suggest that GV can contribute to endothelial damage that could lead to vascular complications as the result of increased inflammation.[18,33]

In comparison to CGM studies, both Kilpatrick et al. and Lachin et al. assessed seven-point glucose profiles from the DCCT cohort and found that, when adjusted for HbA1c, there was no association between SMBG GV and microvascular outcomes, including retinopathy.[34,35] However, a more recent analysis of DCCT data has shown a microvascular relationship with TIR, which is a new measure that takes into account both mean glucose levels and GV.[23]

6 | GLYCAEMIC VARIABILITY AND MACROVASCULAR OUTCOMES

Evidence of an association between GV and macrovascular complications has not been explored in long-term studies and is thus not yet available. Most studies to date include participants with T2DM rather than T1DM, and have reported data concerning HbA1c or four- or seven-point glucose-profile variability rather than the gold standard of CGM-derived measures of GV.[36-38] GV after acute stroke, according to four-point glucose profiles, has been associated with increased CV events and mortality.[39] GV measured using MAGE has been associated with a 10-year CV risk, while GV according to seven-point profiles, SD and CoV, has been associated with QTc prolongation in those with

T2DM.[40,41] Intervention studies would provide much needed insight into the relationship between GV and long-term outcomes; we are not aware of any intervention studies to investigate the long-term impact of CGM-derived measures of GV in T1DM. In T2DM, investigators of the HEART2D study could not show any CV benefits as the result of tightly controlling variations in post-prandial glucose.[42] However, recent publications have highlighted a growing understanding of GV as a key determinant of glycaemic control and are begining to establish a link between GV and the vascular complications of diabetes.[24,43]

Recent studies such as the ACCORD, ADVANCE and DEVOTE trials have demonstrated a relationship between severe hypoglycaemia and CV mortality; however, given the link between GV and hypoglycaemia, it is difficult to determine whether GV and hypoglycaemia are independent risk factors for CV disease, or whether the impact of GV or hypoglycaemia is mediated through the other.[43-45]

In terms of mechanisms for the potential relationship between GV and adverse cardio-metabolic outcomes, in vitro studies have demonstrated a relationship between glucose excursions, collagen synthesis and accelerated apoptosis, with oxidative stress proposed as the key driver of adverse outcomes.[46-48] However, studies in humans have been less conclusive.[18,49,50]

7 | GLYCAEMIC VARIABILITY AND QUALITY OF LIFE

Anecdotally, individuals with T1DM often report that high levels of GV have a negative impact on mood and QoL; however, there are limited studies that support this claim. Despite initial reports of an association between reduced CGM-derived measures of GV and improved diabetes-related QoL and treatment satisfaction, more recent studies have not confirmed the association.[51] In 2015, Reddy et al. reported the largest study of GV and QoL to date in 57 patients with T1DM, using blinded CGM. They found no association between QoL and GV.[52] Although findings may be limited by the exclusion of those with problematic hypoglycaemia and a cross-sectional snapshot of blinded CGM data, it is possible that the diabetes QoL scale employed may be too blunt to assess subtle changes in mood in response to fluctuations in glucose. It would also be of interest to repeat this study with participants unblinded to their CGM data. Overall, CGM use has been associated with improved QoL,[53] and reduced GV may be the mediator. This is an area of interest and further studies are required to investigate the psychological impact of GV.

8 | EVOLUTION OF GLUCOSE MONITORING

The past five decades have witnessed an evolution in glucose-monitoring technology. In the 1950s and 1960s, individuals living with diabetes relied on urine glucose measurements to guide therapy; use of SMBG was not widespread until the 1980s. Despite the fact that intermittent SMBG provides limited information concerning overall glucose profiles and no information concerning the direction of glucose change, it is still accepted as the standard of care, with many international organizations recommending frequent glucose monitoring.[54] Greater frequency of SMBG has been correlated with lower HbA1c, based on observational data that those performing SMBG three to four times daily had HbA1c levels in the range of 8.0%-8.5%, compared to HbA1c levels in the range of 7.0%-7.5% in those performing SMBG seven to nine times daily.[55]

9 | CONTINUOUS GLUCOSE MONITORING: DRIVING A CHANGE IN T1DM CARE

CGM was introduced in the late 1990s and is changing the management of T1DM. Since then, there has been a proliferation of available devices, with each subsequent generation improving in user friendliness, accuracy and often price, in comparison with previous devices. CGM measures glucose in the interstitial fluid, and two main categories of CGM devices exist: real-time CGM (rtCGM) and intermittently viewed CGM (iCGM). Real-time CGM devices include an alarm to warn users if glucose is trending towards hypoglycaemia or hyperglycaemia and they provide near-real-time glucose data. By contrast, with iCGM, glucose information and trends can be viewed only after physically scanning the sensor.

During the past few years there has been an exponential rise in the use of CGM systems; uptake has increased from 7% to 30% from 2010/12 to 2016/18 in the cohort followed in the T1D Exchange trial in the USA.[8] The ability to check and react to glucose readings more frequently, and the existence of alarms that warn users of high or low glucose values, lead to benefits in glucose control, typically a 0.3%-0.5% reduction in HbA1c and a significant reduction in the incidence of hypoglycaemia.[56-58]

10 | DOES CONTINUOUS GLUCOSE MONITORING CONTRIBUTE TO MAKING GLYCAEMIC VARIABILITY THE NEW TREATMENT TARGET?

Increasing access to CGM devices throughout the world is altering fundamentally our approach to T1DM care. Individuals with diabetes, as well as healthcare professionals, are now seeing the complete 24-hour glucose profile, with all the variability entailed. As we begin to understand the variability in glucose, the aim of therapy is shifting towards reducing extreme excursions and maximizing TIR. Recent recommendations from the International Consensus on Time in Range lay out target values for time in and below range in different age groups, recommending a target of 70% TIR for most individuals with insulin-treated diabetes, and aiming for under 4% of time below 70 mg/dL.[22]

GV is an important diabetes outcome in its own right. However, to target a reduction in GV, we first require better access to rtCGM and iCGM for individuals living with T1DM, to enable the routine measurement of GV in clinical practice. Without this, users will fail to gain detailed insight into the presence of GV. Both rtCGM and iCGM are powerful therapeutic interventions. They have consistently demonstrated a reduction in GV in RCTs in addition to

hypoglycaemia and, in the case of rtCGM, in HbA1c.[5,56-59] By allowing users to view daily fluctuations in glucose levels, they make possible the adaptation of both behaviour and insulin therapy to improve these levels.

Historically, rtCGM RCTs have focused on the use of CGM in users of continuous subcutaneous insulin infusion (CSII). However, recent trials such as the DIAMOND, GOLD and HypoDE studies demonstrated that the benefits seen in these earlier CGM/CSII trials are not specific to CSII therapy.[56-58] The addition of CGM to multiple daily injection therapy has been shown in several studies to result in significant reductions in GV, HbA1c and/or hypoglycaemia.[7,56-58] CGM is a robust tool that can support therapeutic decision-making and targets a reduction in GV by allowing it to be measured.

11 | POTENTIAL THERAPEUTIC SOLUTIONS: CAN WE GET BETTER RESULTS BY CHANGING THERAPY?

The challenge in treating T1DM with exogenous insulin and minimizing GV is to mimic control of two physiological processes with different time signatures and target tissues, that is, post-prandial surges in the peripheral circulation and regulation of continuous hepatic glucose output. Therefore, the focus has been on creating fast-acting, short-duration subcutaneous insulin to simulate prandial pulses (bolus) and long-acting, flat-profiled insulin to provide tonic suppression of hepatic gluconeogenesis (basal).

12 | FAST-ACTING ANALOGUE INSULINS

Several fast-acting insulins with very similar pharmacokinetic and pharmacodynamic profiles are currently available, which act significantly faster (onset, 10-15 minutes; peak, 60 minutes; duration of action, 2-3 hours) than human insulin (onset, 30 minutes; peak, 4-6 hours; duration of action, 8-10 hours). However, they still cannot match the speed of onset or the profile of physiological prandial insulin secretion delivered into the portal circulation.

Fiasp (Novo Nordisk, Denmark) is a commercially available preparation of NovoRapid (Novo Nordisk, Denmark), which is co-formulated with nicotinamide and L-arginine. Compared with conventional insulin aspart, following subcutaneous injection, fast-acting insulin aspart has two-times faster onset of appearance in the bloodstream, two-times higher insulin exposure within the first 30 minutes and at least 50% greater insulin action within the first 30 minutes. These benefits appear to be further enhanced during CSII, with more than 100% greater insulin action within the first 30 minutes with fast-acting insulin aspart as compared with insulin aspart. However, these potential benefits have not, as yet, demonstrated an increased reduction in HbA1c in CSII users.[60,61] Assessment of the potential of these agents to influence GV via improved postprandial glucose excursions requires further study.

Inhaled insulin is another solution to the problem of accelerating delivery of insulin and has a more rapid onset of action, along with the attraction of avoiding injections. However, there are concerns about its effects on lungs and reproducibility of action that have limited its availability and uptake.

13 | LONG-ACTING BASAL ANALOGUES

An ideal basal insulin would maintain stable glucose in the fasting state, with minimal variability and, therefore, minimal risk of nocturnal hypoglycaemia. Studies of basal-insulin analogues have consistently shown benefits in reducing hypoglycaemia, in particular nocturnal hypoglycaemia, and, as such, basal-insulin analogue-based multiple daily injection regimens of insulin detemir and glargine are the preferred treatment for all adults with T1DM.[62]

Further improvements in basal-insulin therapy, second-generation basal-insulin analogues, have focused on increasing protraction to provide a more stable and constant 24-hour profile, with a view to reducing GV and risk of hypoglycaemia. Increasing insulin glargine concentration to 300 U/mL (Toujeo) creates an insulin with a longer and flatter pharmacokinetic/pharmacodynamic profile that is attributed to the increased insulin concentration, thus creating smaller, denser aggregates that dissolve more slowly and predictably, and increase the half-life to 16 hours with a 32-hour biological action.[63] Insulin degludec (Tresiba) underwent a modification that allows the insulin to form microfilament precipitates when injected, slowing the first phase of insulin absorption. Absorbed insulin degludec, as insulin detemir, binds to albumin, creating a slowly mobilized insulin-albumin complex. This multiphase protraction prolongs the half-life to 25 hours with a 72-hour biological action.[64]

These second-generation basal-insulin analogues have been shown in clamp studies to reduce GV and inter- and intraday variability as compared with insulin detemir/insulin glargine 100 U/mL. In a clinical study by Bergenstal et al., insulin glargine 300 U/mL showed an improved CGM 24-hour glycaemic profile as compared to insulin glargine 100 U/mL in patients with T1DM.[65] Head-to-head pharmacokinetic/pharmacodynamic studies comparing insulin degludec with insulin glargine 300 U/mL have produced conflicting data concerning the exact comparative profiles.[66,67] This is probably a function of study design, clamp methodology, timing of test injection and choice of metrics. However, both insulin degludec and insulin glargine 300 U/mL are once-daily basal insulins that reduce GV. In a clinical head-to-head study in insulin-naive patients with T2DM, both insulin degludec and insulin glargine 300 U/mL have been shown to have low and comparable CoV as judged by self-measured plasma glucose (27.6%-28.0% CoV), providing an improvement in GV.[68]

14 | CONTINUOUS SUBCUTANEOUS INSULIN INFUSION

CSII provides continuous infusion of rapid-acting insulin to simulate basal insulin. This is supplemented with bolus doses as required. Data suggest that the average reduction in HbA1c for pump users is 0.5%-

0.8%, with reductions in hypoglycaemia events that may be driven by a reduction in GV.[69,70] These studies were conducted without CGM; thus, information on GV is lacking. The DIAMOND follow-up RCT aimed to investigate the impact of adding CSII therapy to the regimens of those already using CGM and multiple daily injections. Although TIR significantly improved in the CSII arm, GV did not, which probably reflects the increased hypoglycaemia that was experienced in the CSII arm,[71] which was thought to be a reflection of inappropriate management of CSII. Interestingly, use of CSII in Sweden has been associated with a significantly lower rate of CV mortality as compared with use of multiple daily injections; one hypothesis is that this is the result of a reduction in both hypoglycaemia and hyperglycaemia.[11] It is possible, although currently not known, that a reduction in GV can improve CV outcomes. At present CSII uptake in T1DM is geographically variable: 18% in England, 30% in mainland Europe and Scandinavia, and 30%-40% in the USA.[7,72-75]

15 | CLOSED-LOOP SYSTEMS AND GLYCAEMIC VARIABILITY

Automated glucose-responsive insulin delivery systems include low-glucose threshold-based suspension of insulin delivery (MiniMed, Paradigm and Veo, Medtronic, Watford, UK), low-glucose prediction-based suspension insulin delivery (MiniMed 640G, Medtronic; t:slim X2 and Basal-IQ, Tandem Diabetes Care, San Diego, California) and hybrid closed-loop systems (MiniMed 670G, Medtronic), along with several other systems under development, all of which manipulate insulin delivery based on real-time sensor glucose levels.

Threshold-based insulin-suspension systems interrupt insulin delivery when the sensor glucose value reaches a predefined threshold.[76] By contrast, predictive low-glucose insulin suspension technology (PLGS) discontinues basal-insulin delivery when hypoglycaemia is predicted. The results of short-term studies suggest that there is a reduction in hypoglycaemia without deterioration of glucose control. Two studies over 14-21 days evaluated PLGS technology compared with sensor-augmented pump therapy. In one study, no difference in GV was found with PLGS technology,[77] while in the other a small improvement in GV was found.[78]

Closed-loop systems, also called artificial pancreas or automated insulin delivery systems, involve control algorithms that modulate insulin delivery, aiming for near-normal glucose levels while minimizing/improving hypo- and hyperglycaemia.[79,80] While most closed-loop studies have evaluated single hormone insulin-only systems, dual-hormone or bi-hormone systems that deliver both insulin and another hormone, such as glucagon or pramlintide, have also been tested. Because of the delay in onset of action of subcutaneously administered rapid-acting insulin, most closed-loop systems require a hybrid approach, characterized by manual administration of prandial boluses, ideally at 15-20 minutes pre-meal.[79-82] These systems can adapt to day-to-day variations in insulin requirements and, doing so, can reduce GV, especially overnight.

Two recent meta-analyses of RCTs compared artificial pancreas systems with either conventional pump therapy or sensor-augmented pump therapy in outpatient settings.[83,84] Closed-loop therapy is associated with increased time within the near-normoglycaemia range, and with reduced hypo- and hyperglycaemia, while modestly reducing HbA1c levels. However, these two meta-analyses did not address the impact of closed-loop insulin delivery on GV. During a 3-month RCT of day-and-night closed-loop insulin delivery in adults with T1DM, GV, measured both as the SD of the sensor glucose level and as the CoV of the sensor glucose level between days, was significantly lower with day-and-night use of the closed-loop system than with the control system.[79] However, a more recent publication from the same group did not show improvements in GV measures with CoV.[80] Similarly, short-term dual-hormone studies have also reported improvements in GV.[85,86]

16 | ADJUVANT THERAPY

In T1DM, insulin is an essential therapy but, as described, replacement of insulin is a complex intervention with a fine balance among hypo- and hyperglycaemia, poor achievement of HbA1c targets and high levels of GV. An interest in adjuvant therapy that exploits additional pharmacological targets to supplement insulin has been renewed following a number of recent publications, including those on sodium-glucose co-transporter 2 (SGLT2) inhibitors.[87-93] An oral therapy that could reduce GV and improve HbA1c would have an important place in T1DM treatment. Only two products, dapagliflozin and sotagliflozin, have marketing authorization from the European Medicines Agency for use as adjuvant therapy.

17 | METFORMIN

Despite the absence of licencing in the UK for use of metformin in T1DM, estimates suggest that 8% of adults with T1DM in Scotland are using metformin in addition to insulin and up to 15% have received at least one prescription for metformin.[94] The use of metformin in T1DM is recognized by NICE.[62] The evidence for metformin use is based on a number of small studies and is controversial and contradictory. A recent large RCT (REMOVAL), which addressed the use of metformin in individuals with T1DM over 3 years, has cast doubt on the short-term therapeutic benefit of metformin. The primary endpoint of averaged mean carotid intima-media thickness, a surrogate measure of CV risk, was not reached, and changes in HbA1c were insignificant. However, a small but significant reduction in body weight and low-density lipoprotein cholesterol, and a significant reduction in maximal carotid intima-media thickness, a prespecified tertiary endpoint, were recorded, and it has been suggested that these small improvements in CV disease risk factors may confer a CV disease benefit in the longer term. No studies have investigated the impact of metformin on GV in T1DM.[94]

18 | SODIUM-GLUCOSE CO-TRANSPORTER 1 AND 2

Selective SGLT-inhibitor drugs have a well-established role in the treatment of T2DM, improving glycaemic control and CV outcomes.[95-97] The mechanism of action of these drugs is to inhibit renal tubular re-absorption of glucose, promoting glycosuria, which leads to plasma glucose lowering and energy wasting. In T1DM, in which glycaemic peaks significantly contribute to GV and in which SGLT2 expression is upregulated, the SGLT inhibitors are interesting potential therapeutic targets. There are now seven published phase 3 studies concerning SGLT-inhibitors in the T1DM population that demonstrate benefits in individuals with T1DM.[87-92,98]

These studies provide consistent observations that SGLT-inhibitor drugs result in a dose-dependent improvement in HbA1c of 0.35%-0.50%. Data from CGM, derived from all phase 3 studies concerning SGLT2 (Tandem1 and 2, DEPICT-1 and -2 and EASE-2) show a significant increase in TIR and a reduction in GV.[88-91]

We will continue to see developments in insulin technology and insulin delivery that more closely mimic physiological profiles. In addition, and for the first time in 100 years, we may also have adjuvant, non-insulin therapies, which act to modify glycaemia through mechanisms that address GV without increasing the risk of hypoglycaemia.

19 | CHALLENGES OF IMPLEMENTING GLYCAEMIC VARIABILITY AS A KEY MEASURE OF THERAPEUTIC SUCCESS

GV is important; it describes the between-day and within-day fluctuations inherent in T1DM glucose management. Visualizing GV and understanding how we support individuals living with diabetes to assist them in getting off the GV "rollercoaster" is the ultimate aim. However, to do this, GV needs increased recognition as a key therapeutic target alongside TIR and HbA1c. To achieve this, we need reliable, accurate and clinically relevant measures of GV; this will be possible only with improved access to continuous glucose monitoring and, more importantly, clinicians will need to be able to view and easily understand clinically meaningful measures of GV. If we listen to the individuals living with diabetes, we understand that GV does matter. For many, securing funding for CGM is a barrier, as is finding the time and motivation to make the behavioural and therapeutic changes necessary to reduce GV. Overall, we need clinical studies that capture the full impact of GV on QoL. Looking forward, we need clinical trials to assess the short-term impact of GV on psychosocial outcomes and, in the longer term, the impact of GV on micro- and macrovascular disease.

20 | CONCLUSION

Managing T1DM is very challenging. In particular, day-to-day variation in physical activity, food intake and insulin delivery makes matching insulin requirements almost impossible. This dose-vs-requirement mismatch generates unpredictable GV. HbA1c is, and traditionally has been, the focus of therapy, with the attempts to optimize HbA1c, and thus reduce hyperglycaemia, being balanced against the clinical aim of avoiding symptomatic or severe hypoglycaemia. However, with increasing access to CGM, we now have the opportunity to expand the horizons of T1DM care and to focus directly on GV. With clinical consultations and therapeutic agents, we can now target the key glucose metrics: GV, TIR and hypoglycaemia. Use of CGM in clinical practice has clearly shown the magnitude of GV experienced by individuals with T1DM and has given us the possibility of assessing and monitoring interventions to reduce GV and thus improve the outcomes and experience of individuals living with T1DM. Novel therapies (eg, faster prandial insulin, more stable new-generation basal insulins, CSII and adaptive algorithms in closed-loop systems, and adjunctive non-insulin therapies with SGLT inhibitors) have the potential to modify GV.

This is now an exciting moment when objectives, therapies and measurements may be aligned, and a new therapeutic paradigm is possible. The challenge is now to use this opportunity to improve the experience, safety and outcomes - the very definition of high-quality healthcare - for all individuals living with T1DM.

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AUTHOR CONTRIBUTIONS

E. G. W., P. C., L. L. and M. B. contributed equally to the outline, research, writing, data analysis and interpretation for this review. All authors critically reviewed and approved the final manuscript prior to submission.

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