Glucose monitoring in diabetes: from clinical studies to real-world practice

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Abstract
Lowering glucose levels in diabetes prevents microvascular complications and long-term macrovascular disease. HbA_{1c} has long been used to guide management decisions, but it fails to address hypoglycaemia and glycaemic variability, both of which are associated with adverse clinical outcome.

While self-monitoring of blood glucose (SMBG) has had a pivotal role in improving glycaemia in diabetes, it provides incomplete glucose data and can be inconvenient to patients. Continuous glucose monitoring (CGM) has the advantage of greater convenience, comprehensive glucose measurements and hypoglycaemia alarms; the latter are particularly useful in individuals with hypoglycaemia unawareness. However, these devices are relatively expensive, limiting widespread use, and most require continued capillary glucose testing for calibration.

The newer flash continuous glucose monitoring (FCGM) device has the advantage of lower costs, long sensor life and factory calibration, negating the need for routine SMBG. However, the lack of hypoglycaemia alarms can be an issue, although a newer generation of sensors will have alarm capability but yet to be released in the UK. Studies have conclusively shown that CGM and FCGM improve glycaemic parameters in individuals with type 1 diabetes, and studies in type 2 diabetes are also promising but limited to draw definitive conclusions on the best subgroup(s) to benefit from this technology.

Despite some reluctance to use CGM and FCGM due to costs and lack of familiarity, there has been a gradual shift from SMBG to these newer glucose monitoring strategies in those with type 1 diabetes, thus improving glycaemic control and the quality of life of these individuals.

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Key words
glycaemic control; hypoglycaemia; glycaemic variability; continuous glucose monitoring

Introduction
Both type 1 (T1DM) and type 2 diabetes mellitus (T2DM) are prevalent worldwide, with an increasing recognition of the need for new strategies to manage these conditions to reduce associated complications.[1,2] It is acknowledged that optimising glycaemic control by reducing glucose levels, while avoiding hypoglycaemia and keeping glucose variability to a minimum, helps prevent consequent vascular complications.[3] Glycaemia remains one of the most difficult risk factors to manage in individuals with diabetes due to the inter- and intra-personal variability in glucose levels in response to a number of routine daily activities such as exercise and diet. Glycated haemoglobin A_{1c} (HbA_{1c}) has long been the standard measure of glycaemic control but has fundamental flaws (detailed below). Self-monitoring of blood glucose (SMBG) has been used for a number of years and does overcome some of the drawbacks of HbA_{1c} but has its own issues, including sporadic glucose data and patient inconvenience. More recently, continuous glucose monitoring (CGM) and flash glucose systems (FCGM) have provided new promise to the management challenges and have potential for improved engagement of patients with their diabetes.

This review aims to: explore glucose monitoring in the context of glycaemic control, and the benefits and disadvantages of glucose testing devices including SMBG, CGM and FCGM; and assess their potential impact in clinical practice moving forward.

The role of glycaemia in diabetes complications
Hyperglycaemia
Hyperglycaemia as a result of diabetes is well acknowledged to have a direct effect on both micro- and macrovascular complications, in the short and long term, respectively.[1–3] Pathophysiological mechanisms for these

complications include increased oxidative stress, enhanced mitochondrial superoxide production and endothelial dysfunction contributing to an inflammatory and thrombotic environment.[4] As a result, attempts to improve glycaemia in order to reduce vascular complications have been comprehensively studied in a range of individuals with diabetes.

The Diabetes Control and Complications Trial (DCCT), involving 1441 T1DM patients, showed that a 1.7% reduction in HbA1c results in decreased microvascular complications over a 6.5-year median follow up, with benefits such as reductions in albuminuria evident as early as one year.[5] The extended study, Epidemiology of Diabetes Interventions and Complications (EDIC) analysing 10-year follow-up data, further demonstrated a clear reduction in macrovascular complications in those who had tight glycaemic control as a result of early and rigorous intervention for hyperglycaemia.[6] The more recent 30-year follow up of DCCT-EDIC showed similar data, emphasising the importance of early glycaemic control for the prevention of long-term macrovascular disease and giving rise to the concept of 'metabolic memory'.[6,7]

In patients with T2DM, similar results have been reported. The UK Prospective Diabetes Study (UKPDS) of newly-diagnosed T2DM patients has shown that intensive glycaemic control reduces both early and late micro- and macrovascular complications, respectively;[7] it is worth noting that the difference in HbA1c comparing two study arms was lower than DCCT at 0.9%.[5–7]

While the aforementioned studies demonstrated a clear benefit of early control of glycaemia, concerns have been raised in relation to tight glycaemic control. The ACCORD study demonstrated increased mortality in the tighter-controlled glycaemia arm, with hypoglycaemia implicated as a possible explanation, though never proven.[8,9]

HbA1c has long been established as the principal measure of glycaemic control, yet there are a number of fundamental limitations that must be acknowledged. HbA1c represents average glucose concentrations over a period of time, yet this average can hide large fluctuations in glucose levels, failing to reflect some high glucose levels that can be harmful.[10] Also, HbA1c does not address hypoglycaemia and glycaemic variability, both of which are associated with adverse clinical outcome.[11–13] Moreover, individuals differ in their glycation potential with 'high glycators' displaying raised HbA1c for relatively minor elevation in glucose levels while 'low glycators' can have acceptable HbA1c despite high glucose levels. A particular issue with the former group is that over-treatment of high HbA1c can result in frequent hypoglycaemia with unintended adverse clinical outcome.[14] Finally, HbA1c values can be misleading in the presence of comorbidity with blood abnormalities including iron-deficiency anaemia and end-stage renal failure.[15,16]

We should therefore recognise the importance of additional glucose assessment in the context of these limitations.

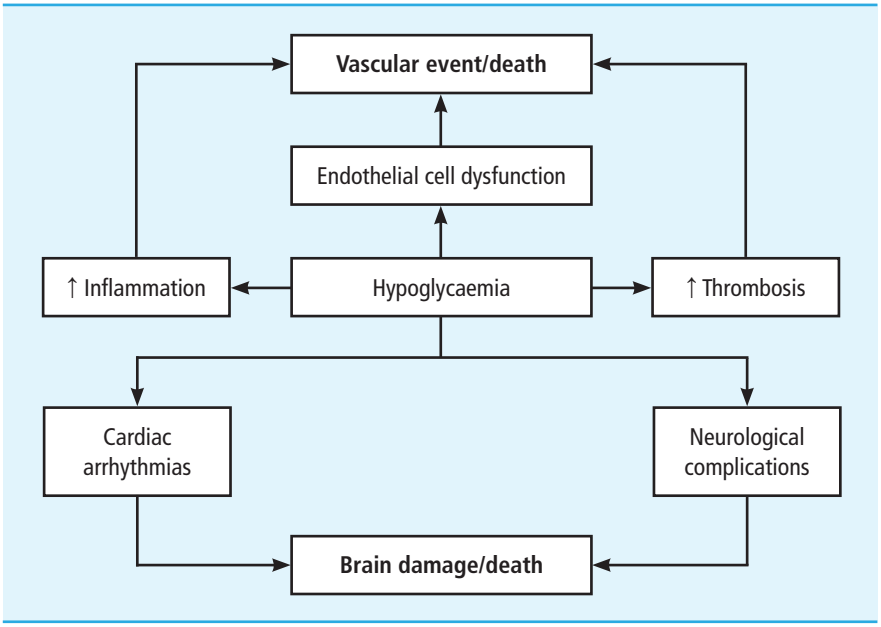

Figure 1. Possible mechanisms for the short- and long-term adverse effects of hypoglycaemia. Mortality secondary to severe hypoglycaemia can be early, secondary to cardiac arrhythmias or neurological complications, or late due to an enhanced inflammatory-thrombotic environment

Hypoglycaemia

The drive for tighter glycaemic control has led to an increased prevalence of hypoglycaemia, which has shown an association with increased mortality.[17–20] A number of mechanisms have been implicated including: cardiac dysrhythmias; increased production of vascular inflammatory molecules; and enhanced thrombotic environment[13,21] (summarised in Figure 1). Additionally, the problem with hypoglycaemia may have a greater prevalence than previously recognised, as SMBG fails to capture all episodes of low glucose levels due to individuals 'treating' these events without testing, or hypoglycaemia may simply go unnoticed in those with impaired awareness.[19,20] Given the aforementioned failure of HbA1c to identify hypoglycaemia and the limited value of SMBG, continuous monitoring of glucose levels is the best alternative to capture hypoglycaemic events but this method has cost implications and some systems can be inconvenient to use. There is a clear need for the introduction of new, affordable and user-friendly devices that give a comprehensive assessment of glucose patterns.

Glycaemic variability

Large glycaemic variability (GV) in diabetes is associated with adverse micro- and macrovascular clinical outcomes both in the short and medium term. Suggested mechanisms for this include increased oxidative stress and excess production of proteins implicated in vascular pathology.[22]

Until recently, we have lacked accurate measures of GV; CGM or FCGM now allow measurement of glucose levels 24 hours/day, which

led to the development of a number of GV measures.[23] Glycaemic coefficient of variation (CV) has been increasingly used as a simple yet reliable measure of GV[24,25] and has shown correlations with diabetes complications.[23] One difficulty with GV is the documented association with hypoglycaemia, making disentangling its direct role in diabetes complications problematic. Further CGM studies will provide more accurate and standardised information on GV, helping to fully understand the role of this glycaemic variable in diabetic vascular disease.[25,26]

Table 1 summarises the role of different glycaemic variables in diabetes complications.

	Hyperglycaemia	Hypoglycaemia	Glycaemic variability
Pathogenic mechanisms	Oxidative stress, enhanced mitochondrial superoxide production and endothelial dysfunction	Cardiac dysrhythmias, increased production of vascular inflammatory molecules and enhanced thrombotic environment	Oxidative stress, excess expression of proteins associated with vascular disease
Clinical studies	Lowering glucose levels reduces complications (DCCT,[5] DCCT-EDIC,[6] UKPDS[7])	Hypoglycaemia is associated with increased mortality (ACCORD,[8] Khunti *et al.*[12])	Large clinical studies showing an association with adverse outcome are lacking
Management strategy	Glucose monitoring (SMBG, CGM and FCGM) and clinical input	Regular glucose testing; most improved with CGM and FCGM	Likely improved with CGM and FCGM

CGM = continuous glucose monitoring; FCGM = flash continuous glucose monitoring; SMBG = self-monitoring of blood glucose.

Table 1. Hyperglycaemia, hypoglycaemia and glycaemic variability in diabetes. Summary of the role of these glycaemic parameters in diabetes complications and the main studies demonstrating an effect on clinical outcome

Glucose testing in optimising glycaemia

Given the limitations of HbA1c, assessment of glucose control should be complemented with SMBG, CGM or FCGM, particularly in individuals treated with agents that may cause hypoglycaemia.

Blood glucose measurement using SMBG

SMBG is the most well-known of the glucose testing methods, given familiarity and ease of patient training. It is relatively inexpensive and gives accurate capillary glucose concentrations, except when using test strips that lack adequate quality control.[27,28] While frequent SMBG is associated with improved diabetes control, repeated testing can be painful, inconvenient to patients and difficult to maintain in the long term.[29–31] In addition, SMBG data may be incorrectly manually entered, whether accidentally or purposefully, which may have serious clinical consequences. Also, some individuals only test when feeling unwell, increasing the possibility of recording very high or very low glucose readings, thus skewing the data and making patients frustrated, which can lead to disengagement.

Interstitial glucose measurement using CGM

CGM is considered to be an improvement over SMBG as it provides comprehensive interstitial glucose data and addresses hypoglycaemia as well as glucose variability.[26,32,33] Systems consist of either 'real-time' data or retrospective readings that can be downloaded in bulk at a later date.[26,29] Real-time CGM has the advantage of an alarm system to alert patients to hypoglycaemia, particularly in those with hypoglycaemia unawareness.[29] Retrospective CGM tends to be used on an intermittent basis with the patient blinded to glucose readings, predominantly to aid diagnosis and perhaps in older patients with insulin-treated T2DM less confident in making management decisions and alterations without discussion with their clinical team.[26,29]

CGM has clear benefits in children and young people with T1DM, with studies[34,35] demonstrating improvements in glycaemic control and reduction in hypoglycaemic events. In general, studies comparing real-time CGM with SMBG in T1DM demonstrated a 0.26% reduction in HbA1c with no additional hypoglycaemia.[36,37] In contrast to T1DM, CGM studies in patients with T2DM have been limited and, although these show potential benefit, more work is required before robust recommendations can be made on the routine use of CGM in T2DM individuals.[25,29]

More comprehensive assessment of glycaemia using continuous glucose testing allowed the assessment of time in range (TIR) as a glycaemic marker involved in diabetes complications. A recent study has shown an inverse correlation between TIR and severity of retinopathy in over 3000 individuals with T2DM, which was still evident after controlling for a number of confounders including HbA1c.[38]

Despite the discussed advantages, some health care professionals (HCPs) have reservations about CGM. At present, CGM is more expensive than traditional SMBG and is comparatively more complex to understand, requiring further training and familiarisation.[26,39] It does require a greater degree of compliance and interaction from the patient, though this may be beneficial in terms of engagement with diabetes management. The continuously attached sensor may be an issue for some patients while others may find the need for sensor replacement every 3–10 days inconvenient. Implantable glucose sensors that can last up to 180 days have been developed but these require a minor procedure for insertion/removal, adding to the cost, complexity and inconvenience.[40]

Most CGM devices require calibration with capillary glucose testing, which can prove inconvenient and has the potential to affect accuracy if not conducted regularly.[41] A recent addition to

the range is the G6 CGM that does not require calibration, has high accuracy and the sensor lasts up to 10 days, although costs may limit widespread use.[42]

Interstitial glucose measurement using FCGM

FCGM is a relatively new form of CGM, released in the UK in 2014, and allows measurements of interstitial glucose every minute, with readings recorded every 15 minutes. Due to factory calibration, there is no need for routine capillary glucose testing and there is a greater duration of sensor life, at two weeks, allowing less frequent changes and reducing impact on patient lifestyle. Additionally, costs are significantly lower than conventional CGM. Currently, there are two available devices: FreeStyle Libre and Libre Pro.[41] The former provides instant glucose data whereas the latter, which is not available in the UK, is a blinded sensor with 14 days' data analysed retrospectively.

FCGM provides extensive data in the form of instant glucose readings and trend arrows along with longer-term data summarised in ambulatory glucose profile (AGP). The AGP can be beneficial to patients and clinicians when making management decisions in terms of changes to improve TIR without increasing hypoglycaemic events.[41,43] The system also provides patients with the independence and education on glucose patterns, particularly in response to individual lifestyle needs. Moreover, the device can act as a blood glucose and ketone monitor negating the need to carry two devices. Accuracy is similar to that of existing CGM devices but one disadvantage is the lack of hypoglycaemia alarms.[41,43] However, it has been confirmed that the next generation sensors will have the option of an inbuilt alarm, and are already in use in some European countries but are not expected to be released in the UK before the second half of 2019.

The IMPACT study has shown a significant reduction in hypoglycaemia with the use of FCGM in T1DM individuals having a well-controlled HbA1c.[43] In the REPLACE study including insulin-treated T2DM individuals with suboptimal HbA1c, FCGM significantly reduced hypoglycaemic exposure but had no effects on HbA1c. However, in a pre-specified subgroup analysis of patients younger than 65 years of age, a significant reduction in HbA1c was noted, suggesting a benefit for the device on this glycaemic marker in younger T2DM individuals.[41] It is worth noting that the reductions in hypoglycaemia in both studies happened despite the aforementioned lack of hypoglycaemia alarm in the system. A criticism of IMAPCT and REPLACE is the lack of a 'treat to target' approach or an educational programme, which may have shown greater benefit for the device.[41,44] The counter-argument, however, is that the improvement in glycaemic parameters occurred without any additional training, and therefore the effects observed were directly related to the device.

Real-world data collected from over 50 000 FreeStyle Libre devices, and including around 64 million glucose readings, demonstrated an average glucose testing of 16 times/day. Moreover, there was an inverse correlation between the number of glucose checks and time spent in both hyperglycaemia and hypoglycaemia.[45] A recent longitudinal study has shown that the largest improvement in hypoglycaemia occurred in the first 72 hours of device wear, indicating this was purely patient-driven. In contrast, the improvement in hyperglycaemia takes around 50 days, suggesting it was due to the combined input of patient and HCP.[46]

The single randomised study with FreeStyle Libre Pro to date, involving insulin-treated T2DM patients in primary and secondary care settings, has shown that intermittent use of this sensor is associated with a significant reduction in HbA1c at three months which is sustained for six months and beyond.[47] However, this was a relatively small study and further work using a larger number of patients, allowing analysis of patient subgroups, is required to fully understand the role of FreeStyle Libre Pro in the management of T2DM.

The improved accuracy of interstitial glucose monitoring devices, the lack of need to calibrate with some, and the reduction in costs make this technology a credible alternative to SMBG. These devices help to optimise glucose levels while improving patient quality of life both by making glucose testing easier and by delaying/preventing diabetes complications.

	Advantages	Disadvantages
SMBG	• Familiarity • Easy to use and train patients • Relatively cheap • Accuracy of capillary glucose measurements	• Subject to user error or incorrectly recorded data • Can be inconvenient and painful • Difficult to maintain frequent testing long term • Limited and sporadic data
CGM	• Comprehensive glucose data • Alarm system for hypoglycaemia • No missed recordings • Encourages patient engagement • Improved glucose control/QoL	• Relatively expensive • Lack of familiarity • Most devices require calibration • Requires patient compliance/training • Requires HCP training
FCGM	• No need for calibration • Extensive glucose data • Greater duration of sensor life • No missed recordings • Encourages patient engagement • Improved glucose control/QoL • Cheaper than CGM devices	• Current devices lack hypoglycaemia alarms (devices with alarm have been announced but are yet to be released in the UK) • More expensive than SMBG • Lack of familiarity • Requires patient training • Requires HCP training

HCP = health care professional; QoL = quality of life.

Table 2. Advantages and disadvantages of self-monitoring of blood glucose (SMBG), continuous glucose monitoring (CGM) and flash continuous glucose monitoring (FCGM)

Table 2 summarises glucose testing strategies in diabetes.

The role of education

With the increasing use of CGM and FCGM, there is a greater opportunity for patient engagement. However, using these devices to optimal benefit requires adequate and thorough patient education. This includes explaining AGP, interpreting glucose data and trend arrows. There is, equally, an importance in ensuring sufficient training for HCPs in device use and data interpretation, both in primary and secondary care settings.

Therefore, education programmes should be developed for patients and carers in order to maximise the benefits of such devices.

The role of CGM in the management of individuals with diabetes is often acknowledged in clinical guidelines such as those from the National Institute for Health and Care Excellence[48] and is further stressed in the Endocrine Society Clinical practice guideline.[49] More robust patient education will improve the potential benefit of these devices and also encourage patient engagement and motivation.

Conclusion

Over the course of the past few years, significant advances in developing CGM and FCGM devices have paved an encouraging path for patients with T1DM and T2DM alike. Current evidence indicates that the majority of T1DM individuals would benefit from CGM/FCGM, with subgroups of insulin-treated T2DM patients also showing potential benefits, particularly when using FCGM in those younger than 65 years.

Thorough and widely-available education for patients and HCPs alike will be required to ensure maximal benefit from the new devices. It should be noted that quality of life and treatment satisfaction measures often improve with the newer glucose monitoring strategies, but this is often ignored when making funding decisions. More focus should be given to patient-reported outcome measures when deciding on implementation of new technologies in diabetes.

Moving forward, there is a need for more studies to characterise patient groups that would benefit the most from CGM and FCGM, in the form of randomised controlled trials and real-world observational studies. Also, the constant development of these devices will further improve accuracy and reduce costs, allowing for these glucose monitoring strategies to gradually replace SMBG. The widespread use of CGM and FCGM coupled with appropriate educational programmes will help to optimise glycaemic control in individuals with diabetes, thus reducing complications and improving quality of life, in addition to decreasing long-term health costs.

Key points

- Traditional use of HbA_{1c} as a measure of glycaemic control has a number of limitations, including the inability to assess hypoglycaemia and glycaemic variability which are associated with adverse clinical outcome
- While self-monitoring of blood glucose has a key role in diabetes management, particularly in insulin-treated individuals, continuous glucose monitoring (CGM) and flash glucose monitoring (FCGM) give more comprehensive glucose data and are associated with improvement in patient quality of life
- Evidence suggests the majority of type 1 diabetes individuals benefit from CGM/FCGM, with subgroups of those with type 2 diabetes also showing a benefit, but studies are limited to draw definitive conclusions
- More work is needed to assess the role of structured education on further improving glycaemic control in CGM/FCGM users, and studies are required to identify the subgroups of type 2 diabetes individuals who would benefit the most from this glucose monitoring strategy

Declaration of interests

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