Clinical Aspects of Continuous Glucose Monitoring

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Abstract

In patients with diabetes, strict glycaemic control is warranted to achieve an improvement in metabolic outcome. When performing self-monitoring of blood glucose, hypo- and hyperglycaemic excursions can be missed. Continuous glucose monitoring (CGM) provides a complete picture of the patient's glucose levels throughout the day. CGM may also warn against impending glycaemic excursions, thereby reducing the fear of hypoglycaemia and improving the patient's quality of life. Patients with brittle diabetes, hypoglycaemia unawareness or gastroparesis, pregnant women with diabetes and those who are critically ill may particularly benefit from CGM. Patients and care-givers must be highly motivated, technologically adept and aware of the limitations of CGM devices to successfully use this type of monitoring in daily practice. The impact of CGM on metabolic control, incidence of hypoglycaemia, chronic complications and quality of life needs further investigation.

Keywords

Continuous glucose monitoring (CGM), diabetes, metabolic control

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More than 15 years have elapsed since the publication of major studies that clearly demonstrated the benefit of aggressive glycaemic control in persons with diabetes.[1–3] Currently, frequent self-monitoring of blood glucose (SMBG) is required to achieve tight glycaemic control.[4] However, SMBG does not provide information about the direction, magnitude, duration, frequency and causes of fluctuations in blood glucose values. Moreover, the fear of hypoglycaemia has a significant impact on patient quality of life and therefore remains a major barrier to achieving optimal glycaemic control. Whereas SMBG takes only a snapshot, continuous glucose monitoring (CGM) provides a complete motion picture of glucose values throughout the day.[5–7] In this way CGM, may prove to be an important asset in future diabetes care. This review addresses advantages and limitations of CGM and the target population.

Advantages of Continuous Glucose Monitoring

Metabolic Control

CGM systems provide the patient and the treating physician with a complete picture of glucose levels throughout the day. They can be used either as a Holter system (retrospectively) or as a realtime monitor.[5–8] CGM readings may facilitate the making of specific therapeutic adjustments to improve metabolic control. These adjustments can be based either on retrospective analysis and pattern recognition or on realtime data verified by SMBG. It will also be possible to take preventative measures by warning the patient against impending hypo- and hyperglycaemic excursions.[8,9]

A number of non-randomised, uncontrolled trials have documented improvement of glycated haemoglobin (HbA_{1c}) and glycaemic excursions (see *Table 1*).[10–19] A total of 13 randomised controlled trials (RCTs) of CGM on metabolic control have been published to date (see *Table 1*).[20–32] In 12 RCTs, HbA_{1c} was used as the primary end-point. Seven RCTs used CGM in retrospect and only one study showed improvement in HbA_{1c} compared with standard SMBG monitoring.[23] Five RCTs used realtime CGM, making dynamic adjustments in insulin therapy based on realtime CGM data and verifying measurements with SMBG. All showed improvement of HbA_{1c} levels compared with standard SMBG, except one.[25] Realtime CGM reduced glycaemic variability and decreased the time spent in hypo- and hyperglycaemia.[21,27,28,31]

Recently, the results of the RCT sponsored by the Juvenile Diabetes Research Foundation (JDRF) were published.[32] In this multicentre clinical trial, 322 adults, adolescents and children with type 1 diabetes who were already receiving intensive insulin therapy were randomly assigned to a group with realtime CGM or to a control group performing SMBG. This study showed a significant between-group difference in the change in HbA_{1c} from baseline to week 26 in patients who were 25 years of age or older, favouring the CGM group (-0.71 versus -0.35%).[32] In addition, more patients in the CGM group had a relative reduction of 10% or more in mean HbA_{1c} levels and a higher number achieved the target HbA_{1c} level of <7.0%. The percentage of time per day within the target glucose range of 70–180mg/dl was significantly greater in the CGM group. Among patients who were 15–24 years of age, no significant differences in any of the glycaemic measures were observed between groups.[32] However, only 30% of these patients used CGM on six or more days per week compared with 83% in patients 25 years of age or older. Among patients who were eight to 14 years of age, the mean decrease in HbA_{1c} levels was 0.38% in the CGM group, which did

Table 1: Metabolic Control Using Continuous Glucose Monitoring

Study	Type of Study	CGM Device	Use of CGM	Number of Patients	Length of Study	Δ HbA_{1c} (intervention vs control)	Hypoglycaemia
Bode et al., 1999[10]	Uncontrolled	CGMS	Retrospective	9 T1DM adults	10 weeks	-1.3% (p=0.019)	
Kaufman et al., 2001[11]	Uncontrolled	CGMS	Retrospective	47 children	6 months	-0.3% (p<0.04)	
Salardi et al., 2002[12]	Uncontrolled	CGMS	Retrospective	44 T1DM	6 months	-0.43% (p=0.032)	
Schiaffini et al., 2002[13]	Uncontrolled	CGMS	Retrospective	18 children	6 weeks	Δ fructosamine: -19µmol/l (p<0.05)	No. of events: -1.4 event/72 hours
Schaepelynck-Bélicar et al., 2003[14]	Uncontrolled	CGMS	Retrospective	12 adolescents	2 months	-1.55% (p<0.05)	
Garg et al., 2004[15]	Uncontrolled	DexCom implantable	Realtime	15 T1DM adults	3 months	47% less time in hypo- and 25% less time in hyperglycaemia	p<0.05
Garg et al., 2006[16]	Uncontrolled	DexCom STS	Realtime	86 T1DM and T2DM adults	21 days	33% less time in hypo- and 28% less time in hyperglycemia	p<0.05
DirecNet, 2007[17]	Uncontrolled	FreeStyle Navigator	Realtime	30 insulin pump T1DM children	13 weeks	-0.3% (p=0.02)	
Garg et al., 2007[18]	Uncontrolled	DexCom STS	Realtime	47 T1DM adults	12 weeks	-0.4% vs +0.3% (p=0.039)	
Bailey et al., 2007[19]	Uncontrolled	DexCom STS	Realtime	140 T1DM and T2DM adults	12 weeks	-0.4% (p<0.0001)	
Chase et al., 2001[20]	RCT	CGMS	Retrospective	11 children	1 month	-0.36% vs -0.20% (p=NS)	
Chase et al., 2003[21]	RCT	GlucoWatch	Realtime	40 children	3 months	-0.5% vs +0.4% (p<0.05)	
Chico et al., 2003[22]	RCT	CGMS	Retrospective	75 T1DM adults	3 months	-0.8% vs -0.5% (p=NS)	
Ludvigson and Hanas, 2003[23]	RCT/ cross-over	CGMS	Retrospective	27 T1DM adults	3 + 3 months cross-over	-0.41% vs -0.1% (p=0.011)	
Tanenberg et al., 2004[24]	RCT	CGMS	Retrospective	128 T1DM and T2DM adults	3 months	-0.8% vs -0.7% (NS)	Reduced duration hypoglycaemia: 49 vs 81 minutes (p=0.009)
DirecNet, 2005[25]	RCT	GlucoWatch B2	Realtime	200 children	6 months	+0.1% vs -0.1% (NS)	p=NS
Lagarde et al., 2006[26]	RCT	CGMS	Retrospective	27 children	6 months	-0.61% vs -0.28% (NS)	
Garg et al., 2006[27]	RCT	DexCom STS	Realtime	91 T1DM and T2DM adults	10 days	21% less time in hypo- and 23% less time in hyperglycaemia	p<0.0001
Deiss et al., 2006[28]	RCT	Guardian RT	Realtime	81 children and 81 adults	3 months	-1.0% vs -0.4% (p=0.003)	
Deiss et al., 2006[29]	RCT/ cross-over	CGMS	Retrospective	30 children and adolescents	3 + 3 months cross-over	+0.1% vs -0.1% (p=NS)	
Yates et al., 2006[30]	RCT	CGMS	Retrospective	36 children and adolescents	12 weeks	-0.4% vs -0.4% (p=NS)	
Lee et al., 2007[31]	RCT	Paradigm RT (sensor-augmented pump)	Realtime	16 T1DM adults	15 weeks	-2.05% vs -1.08% (p=0.02)	
JDRF, 2008[32]	RCT	DexCom seven, Paradigm RT, CGMS, FreeStyle Navigator	Realtime	322 T1DM adults, adolescents and children	26 weeks	≥25 years: -0.71% vs -0.35% (p<0.001) 15–24 years: -0.17% vs +0.33% (p=0.52) 8–14 years: -0.38% vs +0.11% (p=0.29)	p=NS

CGM = continuous glucose monitoring; CGMS = continuous glucose monitoring system; HbA_{1c} = glycated haemoglobin; JDRF = Juvenile Diabetes Research Foundation; NS = non-significant; RCT = randomised, controlled trial; T1DM = type 1 diabetes; T2DM = type 2 diabetes.

not differ significantly from the control group. However, secondary indices of glycaemic control were improved in the CGM group, with more patients having a relative reduction of 10% or more in HbA_{1c} levels and more achieving the target HbA_{1c} level of <7.0%.[32]

In addition to HbA_{1c}, glucose variability may be an important parameter in metabolic control and even a predictor of diabetic complications.[33] Many hyper- and hypoglycaemic spikes may cancel each other out in terms of altering HbA_{1c} levels. By making therapeutic adjustments based on trend information, realtime CGM may enable patients to reduce glycaemic variability and increase the time spent in normoglycaemia.[17,34] Patients with a wide variability in blood glucose concentrations (brittle diabetes) may especially benefit from the use of CGM. This is because it is often difficult to make appropriate insulin dose adjustments based on SMBG data in the face of their large inter- and intraday variation in glucose readings. For some patients a reduced glycaemic variability alone, even without any improvement in HbA_{1c}, might represent an improved outcome.

CGM can also be applied to identify and treat post-prandial hyper-glycaemia.[35] Post-prandial glucose peaks vary according to meal composition, so the timing of insulin administration has to be optimal. Factors that patients need to take into account before taking extra insulin to treat post-prandial hyperglycaemia include the residual insulin 'on board' from the pre-meal bolus, the direction of the glycaemic trend and the type of carbohydrate in the meal. After eating high-glycaemic-index carbohydrate foods, there is a rapid spike in glucose level. Normally there is enough insulin on board to deal with this glucose peak. Another extra bolus would impose a considerable risk of hypoglycaemia. By contrast, after a low-glycaemic-index meal, glucose absorption tends to be prolonged and an additional bolus may be needed to bring the level down to target.[36] Furthermore, diabetic gastroparesis may complicate optimal timing of insulin administration.[37] Early insulin administration in respect to a delay in glucose absorption causes a sudden drop in glycaemia followed by a hyperglycaemic episode. Realtime CGM can detect post-prandial hyperglycaemia more reliably than SMBG and can be used to match insulin delivery to glucose absorption.[38]

Extreme Glycaemic Excursions/Hypoglycaemia

Hypoglycaemia, in particular nocturnal hypoglycaemia, occurs frequently in patients treated by means of multiple daily insulin injections or by insulin pump.[39–41] Most of these hypoglycaemic episodes are asymptomatic and remain undetected by standard SMBG, as finger-prick glucose measurements are rarely performed at night.

To deal with nocturnal hypoglycaemia, CGM may be used in two different ways. First, CGM can be used in retrospect to identify the incidence and magnitude of nocturnal hypoglycaemia and guide insulin treatment accordingly. Second, most CGM devices can detect impending glycaemic excursions in realtime 20–30 minutes ahead and are equipped with an alarm function. In this way, CGM can warn the patient of emerging hypoglycaemia and allow him or her to take appropriate preventative measures.[8,9] Hyperglycaemic excursions can be identified and dealt with in the same way. The alarm function represents a major advantage for patients with hypoglycaemia unawareness, allowing the patient to feel more confident. This leads to an improvement in the patient's quality of life.[42] Warning the patient against impending hypoglycaemia is especially important when driving and may be an significant tool in preserving the patient's ability to drive.

In the recently published JDRF trial, hypoglycaemic events were infrequent in the two study groups. Only 5–10% of patients experienced at least one severe hypoglycaemic event, with no significant difference between the study groups. Despite this, it is noteworthy that in the CGM group among patients 25 years of age or older a decrease in HbA_{1c} levels was achieved without an increase in hypoglycaemic episodes. This finding is in contrast to those of the Diabetes Control and Complication Trial, which showed an increase in hypoglycaemic events in patients who lowered their HbA_{1c} levels. However, the JDRF trial was not powered to detect a difference in the occurrence of hypoglycaemia.[1,3,32]

Motivational Aspects

CGM may improve metabolic control not only by providing accurate data for the adjustment of insulin treatment but also by promoting communication between the patient and the treating physician. Motivational benefits include reinforcement of educational concepts, enhanced self-efficacy, increased flexibility in daily life and enhanced motivation for better metabolic control.[43] The reduction in fear of hypoglycaemia by using realtime CGM may improve quality of life.

The Diabetes Research in Children Network (DirecNet) received very positive comments from patients using the FreeStyle Navigator CGM system (Abbott). Most subjects used the Navigator on a daily basis. More than 70% of children and their parents agreed that its use made adjusting insulin easier, showing patterns in blood glucose not seen before and clarifying how eating habits affected glycaemia.[25,44]

Limitations of Continuous Glucose Monitoring

Limitations Related to the Device

Currently most available CGM systems are minimally invasive and require the insertion of a needle or a microdialysis catheter into the subcutaneous adipose tissue to measure glucose in the interstitional fluid. Non-invasive CGM systems, such as the GlucoWatch Biographer (Cygnus) and the Pendra (Pendragon Medical), are no longer available and other techniques are at a pre-clinical stage.

After application of the CGM device, a first calibration can only be performed when the sensor signal is stable. A certain amount of time is required for the equilibration process between the analyte and the sensor surface. Depending on the type of sensor, this can take between two and 10 hours.

The CGM sensor needs to be calibrated several times to achieve good accuracy. This is because all sensors exhibit a certain amount of signal drift as the result of a foreign body reaction exerted by the sensor or microdialysis catheter. Such a signal drift can result in a complete loss of correlation between changes in the sensor signal and glucose levels. Compensation of the drift by repeated calibration is possible for a limited period of time.[5] This explains why the use of currently available CGM devices is restricted to only a few days. An advantage of the microdialysis technique used by the GlucoDay device (Menarini Diagnostics) is that the foreign body reaction is limited.

Accuracy also depends on the technological and physiological lag time. The technological lag time is device-specific and depends on sampling frequency, membrane pore size and probe dimensions. In the case of microdialysis-based systems it also depends on dialysis perfusion rate. This lag time seems to be rather consistent, not depending on fluctuations in glycaemia and insulin levels.[45–47] The physiological lag time is the time needed for glucose to equilibrate between the capillary blood and interstitial fluid. This period varies from a few seconds to 15 minutes, depending on peripheral glucose utilisation, capillary blood flow and insulin levels.[48] Therefore, changes of glucose concentrations in interstitial fluid do not occur at the same time as those in the blood; they lag behind. This has important implications on clinical decision-making during times when the glucose level is changing rapidly. For example, when glucose is falling rapidly, the physiological lag time leads to normal sensor glucose readings (interstitial) even when the actual blood glucose level is quite low. Capillary glucose measurements therefore remain necessary.[36]

To optimise CGM accuracy it is important to calibrate the device during steady-state conditions. If glycaemia is increasing rapidly, for example during the post-prandial period, the glucose level in the blood is higher than in the interstitial fluid. If the CGM device were to be calibrated after a meal, this would lead to an upward setting of the

glucose sensor and would compromise the accuracy of the device in detecting hypoglycaemia.

Currently available CGM systems are approved only as an adjunct to standard SMBG and should not be used to make therapeutic decisions without verification by blood glucose measurement.

Limitations Related to the Patient

In contrast to the motivational benefits, realtime CGM may lead to an increased treatment burden and information overload. Some patients may not be able to deal with the additional data and might overcorrect changes in glycaemia. This should be a major focus of education for the patient using realtime CGM.

Poor patient adherence is an important limitation to the use of realtime CGM. The JDRF showed less benefit of CGM among patients who were eight to 14 years of age and no benefit among those 15–24 years of age.[32] This observed age effect may be related to substantially lower use of sensors in the children and adolescent group compared with adults.

Imperfect adherence to many aspects of diabetes management has long been recognised as an obstacle to successful intensive treatment in adolescents and young adults. Greater parental involvement could be the reason why children in the CGM group had greater sensor use than the adolescents. At least six days of sensor use per week was the average for 83% of patients 25 years of age or older, but this percentage dropped in young people to 30% of patients 15–24 years of age and 50% of patients eight to 14 years of age.[32]

It is important to recognise that the participants in the JDRF trial were highly motivated and capable of using CGM technology and had a better than average metabolic control. The results therefore cannot be extrapolated to a random diabetes population.

Target Population

Patients should be well educated in order to safely use and benefit from CGM. They should be very motivated to participate in the management of their diabetes and be technologically adept. By contrast, patients who have poor metabolic control because of reluctance to perform SMBG will not benefit from the use of CGM. Patients should receive proper instructions about the use of their CGM device, calibration issues and therapeutic decision-making.

Patients who may benefit from the use of CGM include:[49]

- patients with brittle diabetes with poor metabolic control and/or high glucose variability;
- patients with hypoglycaemia unawareness and/or fear of hypoglycaemia;
- patients with gastroparesis;
- pregnant women with diabetes; and
- critically ill patients.

CGM may be used as a tool to reduce glycaemic variability in patients with brittle diabetes to increase time spent in the normoglycaemic range and improve metabolic control.[18,34]

In patients with fear of hypoglycaemia and hypoglycaemia unawareness, realtime CGM can be used as a monitor to warn against impending hypoglycaemic events. This allows the patient to take preventative measures.[42]

Patients with diabetic gastroparesis may benefit from CGM to optimise the timing of their insulin administration in order to avoid glycaemic excursions.[38]

For pregnant women with diabetes, strict metabolic control is essential to avoid maternal and foetal complications such as macrosomia, foetal malformations, pre-term delivery and Caesarean section. CGM may therefore help to achieve normoglycaemia, optimise insulin treatment, improve metabolic control and reduce the risk of complications.[50] This is particularly important during the first trimester of pregnancy.[51,52]

Another important and recently highly controversial issue is glycaemic control in critically ill patients. The strict euglycaemic range of 80–110mg/dl, as proposed by the Leuven trials,[53,54] was criticised by more recent studies. Two multicentre studies (VISEP and GLUCONTROL) were stopped prematurely because of safety reasons (more hypoglycaemia) and lack of benefit.[55–57] The NICE-SUGAR study demonstrated increased mortality in the intensive glucose control group (81–108mg/dl) compared with conventionally treated patients (<180mg/dl).[58] However, correct assessment of the magnitude and duration of hyperglycemia is important, and can only be performed using CGM.[59,60] CGM may be beneficial as it enables intensive care unit staff to evaluate the effect of insulin therapy on the patient's glycaemia in real time. With CGM, strict glycaemic control can be achieved without the fear of undetected hypoglycaemic events.

Conclusion

In order to achieve tight glycaemic control, the patient with diabetes needs to perform frequent SMBG. Hypo- and hyperglycaemic episodes can be missed between glucose measurements. Furthermore, the fear of hypoglycaemia has an important impact on the patient's quality of life.

CGM systems provide a complete picture of glucose levels throughout the day and can warn against impending glycaemic excursions. In order to use CGM systems, patients and healthcare providers need to be highly motivated, technologically adept and aware of the limitations. Patients with brittle diabetes, hypoglycaemia unawareness or gastroparesis, those who are pregnant and those who are critically ill may particularly benefit from CGM.

In the future, the incorporation of CGM in a closed-loop system – the artificial pancreas – will be a major breakthrough in diabetes care. For now, CGM may be an aid to achieve adequate metabolic control with peace of mind. ■

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