

Should all patients on insulin be using continuous glucose monitoring?

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Continuous glucose monitoring (CGM) is being used increasingly both in patients on insulin pumps (CSII) and more recently in those on multiple injection regimens (MIR). This review lists the CGM devices available in South Africa and explores the literature supporting the use of CGM as a primary modality for monitoring blood glucose in those with diabetes on MIR. In particular, the role of CGM as a modality for improving glycaemic control and reducing hypoglycaemia is explored. The identification of appropriate patients, the possible barriers to the institution of CGM and the role of CGM in the future of diabetes care is discussed.

Keywords: continuous glucose monitoring, flash monitoring, multiple injection regimens, type 1 diabetes

Introduction

Advances in the management of type 1 diabetes have progressed significantly over the years with the advent of newer insulins, more accurate blood glucose meters, diabetes education and insulin pumps (CSII). However, every few decades a major shift in diabetes management occurs that has the potential to radically change the life of our patients, although it often takes time, even years, for the true impact of these changes to filter through to the medical profession at large. A paradigm shift resulting in a turning point in diabetes management last occurred in the late 1970s with the advent, fairly simultaneously, of self home glucose monitoring (SHBG), insulin pens, the concept of basal/bolus insulin regimens and the early mechanical insulin pumps. All progress since then has been built on those developments, until now. Recently we have been experiencing another seismic shift, which will revolutionise diabetes management going forward.

Continuous glucose monitoring (CGM) has been around for almost two decades¹ but initially made little impact. The devices were not accurate enough and were difficult to insert. More recently, with improved technology, CGM came to be considered an option for patients on CSII, but it is only in the last two years that attention has seriously turned to the efficacy of CGM when used in patients on a multiple injection regimen (MIR).

There are currently four stand-alone (not connected to a pump) CGM devices available in South Africa. These devices all transmit real-time glucose information to the user and have been termed 'Real-Time CGM' (RT-CGM). These are the Dexcom G5 and G6, Medtronic Guardian Connect and Roche Eversense devices. The Freestyle Libre 'Flash monitoring' device, while monitoring glucose continuously, only provides glucose data to the patient when the sensor is scanned ('flashed'). The term 'intermittently scanned CGM' (isCGM) has been coined.²

The essential features and differences between these devices are listed in [Table 1](#).

One of the potential or theoretical problems is that all CGM sensors measure glucose in interstitial fluid rather than capillary blood. It is assumed that with the modern sensors interstitial

glucose measurements can be equated to blood glucose accurately, although few studies have been published using the newer sensors to confirm this. Nevertheless, any time-lag between the two levels is probably not relevant when glucose levels are stable. However, with rapid changes in glycaemia this difference may become more meaningful. With rapid rises in glucose, such as those seen postprandially, the interstitial glucose measurement may be up to 15% lower than the simultaneous blood glucose, whereas with a rapid reduction in glucose the interstitial glucose may read up to 20% higher than the blood glucose.^{3–5} However, a study comparing Flash monitoring with blood glucose levels in 45 Chinese subjects⁶ showed good correlation in glucose readings with an overall between-sensor coefficient of variation of 8.0%, and the mean lag time was only 3.1 minutes. Thus, there may be at least a theoretical risk in adjusting insulin doses based on CGM results. Nevertheless, it seems that the current accuracy of CGM is sufficient to allow for safe adjustment of insulin doses.^{7,8} It has also been demonstrated that isCGM (Flash monitoring) is at least as accurate as RT-CGM^{8–11} with no significant difference in the estimation of clinical diagnostic parameters. Flash monitoring has also been shown to be accurate enough for clinical purposes in children¹² and pregnant women.¹³ While the Flash monitoring system is factory calibrated and does not require fingerprick glucose to calibrate, it is recommended that the value be confirmed by fingerprick during rapidly changing glucose values, to confirm sensor-reported hypoglycaemia or impending hypoglycaemia, and also if symptoms do not correspond to the glucose value displayed.

CGM in type 1 patients on MIR

The role of CGM in patients on continuous subcutaneous insulin infusion (CSII) using insulin pumps is well established.¹⁴ However, it has only been in the past few years that CGM has been utilised with multiple insulin regimens. One of the earlier reports on the effectiveness of CGM in patients on MIR was the JDRF Trial¹⁵ in 2008, which involved 322 adults and children, but more than 80% of these subjects were on CSII. The COMISAIR Study (Comparison of Different Treatment Modalities for Type 1 Diabetes, Including Sensor-Augmented Insulin Regimens)¹⁶ included 65 type 1 patients followed up for a year, of whom 27 were on CGM, but only 12 of these were on MDI and not

Table 1: Features of available CGM devices

Device	Sensor life	Need for fingerprick calibration	Essential features
Dexcom G5	7 days	2x daily (12 hourly)	Receives glucose levels continuously on smartphone—they are automatically sent every 5 minutes to a mobile phone Receives customised alerts when glucose level is rising, falling or reaching pre-set thresholds Enables third person to remotely see the glucose value in real time, or notifies them by SMS in case of hypo events
Dexcom G6	10 days	none	Receives glucose levels continuously on smartphone—they are automatically sent every 5 minutes to a mobile phone Receive customised alerts when glucose level is rising, falling or reaching pre-set thresholds Enables third person to remotely see the glucose value in real time, or notifies them by SMS in case of hypo events Will allow for sensor-augmented pump integration
Medtronic Guardian	6 days	2–4x daily	Receives glucose levels continuously on smartphone—they are automatically sent every 5 minutes to a mobile phone Receives customised alerts when glucose level is rising, falling or reaching pre-set thresholds
Roche Eversense	90 days	2x daily	Implanted subcutaneously and replaced every 3 months Receives glucose levels continuously on smartphone—they are automatically sent every 5 minutes to a mobile phone Receives customised alerts when glucose level is rising, falling or reaching pre-set thresholds
Freestyle 'Flash'	14 days	none	Glucose level accessible by passing reader over sensor Trend Arrow provides information as to whether glucose rising, falling or stable Full 24-hour retrospective data available and downloadable but only if sensor is scanned at least every 8 hours No alarms for hypo-or hyperglycaemia

CSII. In both these studies the use of CGM showed an overall significant improvement in HbA1c in those on both CSII and MIR. Of interest, the COMASAIR study found that at 12 months, those on MIR + CGM had very similar HbA1c levels to those using CSII + CGM (7.2% vs 7.1%). The first major study involving CGM in type 1 patients specifically on MIR was the Diamond Study¹⁷ (Effect of Continuous Glucose Monitoring on Glycemic Control in Adults with Type 1 Diabetes using Insulin Injections. The DIAMOND Randomized Clinical Trial). This study was structured to answer the question as to whether adult type 1 patients on MDI will improve their HbA1c levels using CGM. A total of 105 subjects were assigned to CGM using the Dexcom device versus 53 using SHGM, for 24 weeks. With CGM the mean HbA1c reduction from baseline was 1.1% at 12 weeks and 1.0% at 24 weeks versus a mean HbA1c reduction from baseline of 0.5% at 12 weeks and 0.4% at 24 weeks in the SHGM group. CGM metrics for time in the range of 3.9 to 10 mmol/l, hyperglycaemia, hypoglycaemia and glycaemic variability favoured the CGM group compared with the SHGM group. There were no significant differences between the CGM group and control group with regard to median change in total daily insulin dose per kilogram of bodyweight and mean change in bodyweight. Interestingly, the frequency of injections increased from a mean of 3.9 to 6.2 in the MDI group, clearly indicating that patients became more involved in their self-management. These findings were independent of level of education, maths ability and age, suggesting that CGM can be instituted successfully in most patients. However, study protocols included self-management education, and HbA1c reduction tended to correlate with the degree of education received. This highlights the point that CGM may get patients more engaged in their self-care, but also that more engaged and better educated patients benefit most from CGM.

A second large trial, which was published simultaneously with the DIAMOND study, was the GOLD randomised clinical trial.¹⁸

In this study 161 type 1 patients with HbA1c levels of at least 7.5% (mean HbA1c 8.6%) were randomised to CGM or conventional treatment, each for 26 weeks in a crossover design. Mean HbA1c was 7.92% on CGM and 8.35% during conventional treatment. Patients on CGM also had less severe hypoglycaemia despite lower HbA1c levels. It is noteworthy that rates of severe hypoglycaemia increased in the crossover trial when patients switched back to SHGM from CGM. This finding could possibly be explained by the fact that patients on CGM become comfortable setting lower blood glucose targets. They may also depend on blood glucose alerts and live data to make dosing decisions that are more precise and aggressive compared with SHGM.

The efficacy of RT-CGM in reducing hypoglycaemia in patients with severe hypoglycaemia unawareness has recently been confirmed.¹⁹

The above studies all utilised CGM with the Dexcom device. The unanswered question is whether isCGM using the Freestyle 'flash' monitor is able to produce similar results in patients on MIR. In general, patients seem to prefer isCGM because of the perceived ease of use, the removal of calibration by fingerprick and the lesser cost. However, the overall trend is for sensors to become smaller and easier to insert, require less or no calibration and become less costly. The latest Dexcom G6 system for example now offers a 10-day sensor life and no calibration. Another advantage of the Dexcom G6 is that it is the first stand-alone sensor that can be integrated with a pump as part of a sensor-augmented pump solution, may also be used in MIR patients, and can share data with third parties.

A large multicentre comparative trial comparing HbA1c outcomes in those on isCGM versus standard care in patients using MIR has been published.²⁰ This trial enrolled 167 participants with type 1 diabetes and a mean HbA1c of 7.5%, with 82 in the isCGM group and 81 controls. A further publication

on this group, the IMPACT study,²¹ was a pre-specified subgroup analysis specifically designed to investigate use of the Flash system in reducing hypoglycaemia compared with SMBG. As reported in both publications, this study found that the use of Flash glucose monitoring in type 1 diabetes on MDI therapy significantly reduced time in hypoglycaemia with the mean time in hypoglycaemia being reduced by 46.0%, from 3.44 hours/day to 1.86 hours/day in the intervention group compared with a reduction from 3.73 hours/day to 3.66 hours/day in the control group (95% CI -2.21, -1.09; $p < 0.0001$) This was achieved with no difference in HbA1c. However, the mean starting HbA1c in this group of very well-controlled type 1 subjects was 6.8%, leaving little room for further improvement. Time in range was also significantly increased in the CGM group and glycaemic variability was decreased. Patients using the Flash technology reported improved treatment satisfaction and perception of hypo/hyperglycaemia was improved compared with the control group. This reduction in hypoglycaemia mirrors what was reported in the DIAMOND¹⁷ and GOLD¹⁸ studies using RT-CGM. Dover *et al.*²² assessed the real-world effect of Flash glucose monitoring in their diabetes clinic. They placed 25 random participants onto Flash monitoring, of whom 17 were on MIR. After 16 weeks the mean HbA1c of the group dropped from 8% to 7.5% with the number of people with an HbA1c $\leq 7.5\%$ more than doubling. Episodes of hypoglycaemia (glucose < 4 mmol/l) reduced from 17 in the first 2 weeks to 12 in the last 2 weeks with a significant reduction in the Diabetes Distress Scale. A number of additional studies have confirmed these findings and a full review of these studies has recently been published.²³

As might be expected, in view of the hypoglycaemia alarm function, RT-CGM may reduce time in hypoglycaemia more effectively than isCGM in hypoglycaemia-unaware subjects as reported by Reddy *et al.*²⁴ This would support both the view of the French position statement on CGM²⁵ and the NICE position statement,²⁶ which recommend RT-CGM if hypoglycaemia is deemed a major issue in view of the alarm function, and isCGM (Flash) if hypoglycaemia is deemed not to be a significant problem.

Both RT-CGM and isCGM are now considered together as CGM in many guideline documents,^{2,25-27} and many believe that Flash glucose monitoring is the future of glucose monitoring^{23,29} as it does not require fingerprick calibration, is non-intrusive and simple to use, and is less costly than RT-CGM. While the sensor traditionally is inserted at the back of the upper arm, a recent publication by Charleer *et al.*³⁰ has demonstrated that similar accuracy can be obtained utilising the upper thigh, which might make the sensor less visible in summer clothing. Placement of the sensor in the abdomen results in poor performance and should not be encouraged.

The HbA1c has been regarded as the gold standard of glycaemic control and together with SMBG it has been the standard way of assessing glycaemic control.³¹ However, the usefulness of the HbA1c as the primary endpoint of control has come under review.³² With the advent of CGM, recent evidence linking hypoglycaemia with adverse outcomes, and the ability to better assess patterns of glycaemia, other parameters of assessing glycaemic control have been proposed.³³

Hypoglycaemia

With attempts at tighter glycaemic control, hypoglycaemia has become a significant problem, even in those with so-called

'preserved hypoglycaemia awareness'³⁴ and is considered one of the main limiting factors in achieving good glycaemic control.³⁵ The use of CGM allows not only for the detection of asymptomatic hypoglycaemia, but also for the measurement of duration of hypoglycaemia and 'time below range'. While, as outlined above, CGM can significantly reduce time in hypoglycaemia, it has not yet been determined how long in hypoglycaemia should be considered clinically meaningful.

Glycaemic variability

It has been suggested that increased glycaemic variability may be linked to adverse clinical outcomes,³⁶ but the evidence for this is weak. Most studies on glycaemic variability have relied on serial HbA1c levels or SHGM results and neither gives a full picture of variability. CGM allows for a more accurate assessment of glycaemic variability and the possibility of improving this parameter. With its use, a better understanding of the association between glycaemic variability and outcomes will become possible.

Time in range/time above range

Assessing the actual amount spent in a predetermined glycaemic range, usually between 3.9 and 10 mmol/l, taken together with hypoglycaemia data, may be a better indicator of overall glycaemic control than the HbA1c and is relatively easy to determine with most CGM software.

Overall, the type 1 diabetes studies have shown that CGM improves glycaemic control and reduces time in hypoglycaemia, whether patients are on MIR or insulin pump therapy. Further real-life long-term clinical studies are required to be able to identify which patients may benefit most from CGM. A criticism has been one of information overload, but studies have shown no increase in psychosocial stress and patients generally enjoy the process.^{37,38} However, some authors feel this aspect requires more real-life research.³⁹

Type 2 diabetes

There has been much less research conducted into the use of CGM in patients with type 2 diabetes. Findings vary from no effect on glycaemic control to a significant reduction in HbA1c and/or hypoglycaemia.⁴⁰ In an early study, Vigersky *et al.*⁴¹ assessed the efficacy of CGM in 100 type 2 patients receiving various forms of pharmacotherapy including basal insulin but not those on MIR. Compared with SHGM, the intermittent use of CGM resulted in significant improvements in HbA1c sustained for 40 weeks. In the 158 subject type 2 cohort using MIR from the DIAMOND study,⁴² there was a 0.3% reduction in HbA1c at 24 weeks compared with those using SHGM. Although small, this reduction was statistically significant. However, the higher the baseline HbA1c the better was the improvement in control, and those on CGM spent more time in range than those using SHGM. Unlike the type 1 DIAMOND study, there was no difference in hypoglycaemia, which may not be surprising since in the type 2 cohort hypoglycaemia was much less of a problem. On the other hand, a study by Haak *et al.*⁴³ involving 224 type 2 patients from 26 European centres, using Flash glucose monitoring as a replacement for blood glucose monitoring showed no difference in HbA1c but a reduced incidence and duration of hypoglycaemia.

One of the advantages of CGM in type 2 patients may be to stimulate better lifestyle choices, as demonstrated in a study by Allen *et al.*⁴⁴ They used CGM in conjunction with nutritional and exercise feedback in non-insulin-requiring patients and

showed improvements in physical activity and reductions in BMI, as well as a mean 1.16% reduction in HbA1c when compared with SHBGM. A literature review of the use of CGM in type 2 diabetes⁴⁵ concluded that the use of RT-CGM in type 2 diabetes reduced HbA1c, improved patient adherence to diet and exercise regimens, reduced the number of hypoglycaemic events and improved quality of life.

Problems and challenges with CGM

An International Consensus statement published in December 2017²⁸ recommends CGM to be used in conjunction with HbA1c for glycaemic assessment and adjustment of therapy in all type 1 patients and those type 2 patients on MIR. However, while the use of CGM, particularly in those with type 1 diabetes, shows clear advantages, there are certain problems with its wider utilisation. Chief amongst these is the cost. While Flash glucose monitoring is significantly less expensive than RT-CGM and largely does away with fingerprick glucose measurements, and notwithstanding the fact that it is less sophisticated, it is still costly and out of the reach of many patients. The reticence of Medical Aids (Health Insurers) to fund this technology is unfortunate and makes it available only to those who have sufficient personal funds. As far as RT-CGM is concerned, once again the exorbitant cost makes it unaffordable for most. Additionally, the need to calibrate with fingerprick glucose several times a day is unappealing to patients and adds to the cost. Sensor lifetime is a factor that contributes to cost and inconvenience although the Eversense implanted device lasts for three months, which is shortly to be extended to six months. With Flash monitoring, the durability of the adhesive used to attach the sensor to the skin may be problematical⁹ as can be local skin reactions to the adhesive.

Undoubted improvement over time

Currently, Flash monitoring is reimbursed by many funders in Europe and the USA. Unfortunately, this is not yet the case in South Africa.

It is self-evident that measuring blood glucose does not by itself improve any of the parameters of glycaemic control. Without adequate patient education and follow-up, any form of self glucose monitoring is a pointless exercise. This is even more crucial with CGM, be it RT-CGM or isCGM. Interpretation of the glucose profiles, detection and management of hypoglycaemia, attempts to keep glucose 'in range' and avoiding excess variability requires in-depth understanding by both the patient and the healthcare professional, and this level of education is time-consuming for both parties.

One of the biggest barriers to the more universal use of CGM, notwithstanding the above, is a reticence of doctors and healthcare providers to promote this form of management. This may be due to ignorance on the part of the doctors and diabetes nurse educators, or lack of time, or just provider apathy and inertia.

Another issue that has arisen is the lack of standardisation in reporting programmes that makes analysis and comparisons between CGM devices difficult. An Expert Panel⁴⁶ has been convened to provide recommendations in this regard.

Conclusions

The advent of CGM is changing the paradigm in the management of diabetes. Currently it is still regarded by many as new, untested and by some as an 'expensive gimmick'. However,

emerging literature suggests very real advantages. Other than practical limitations of cost and the need for supportive education and counselling, there can be no objection to incorporating CGM in the treatment of every person with type 1 diabetes on MIR. The literature with regard to type 2 diabetes is not as robust at this stage although there seems to be a real advantage for those on MIR.

One can envisage a future where, due to the progressive removal of barriers to CGM such as cost, sensor size, sensor duration, accuracy and requirement for calibration, CGM will become the preferred method of monitoring patients with type 1 diabetes and possibly eventually for those with type 2 diabetes on insulin. The HbA1c is likely to become less important in assessing patient outcomes. Glycaemic variability, time in range and time in hypoglycaemia will become, ever-increasingly, endpoints to be taken into account. SHGM may well become obsolete in future years.

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