Should all patients on insulin be using continuous glucose monitoring?

Larry A Distiller*

Centre for Diabetes and Endocrinology, Johannesburg, South Africa
*Email: larry@cdecentre.co.za

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 decades but initially made little impact. 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 decades but initially made little impact. 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.1-5 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-CGM8-11 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 GGM in patients on continuous subcutaneous insulin infusion (CSII) using insulin pumps is well established. 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
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 ≤ 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 monitoring28,29 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.33 However, the usefulness of the HbA1c as the primary endpoint of control has come under review.34 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 fingerpick 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 fingerpick 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 problematic9 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.

Disclosure statement

Dr Distiller has acted in a consulting capacity for Abbott Pharmaceuticals and Roche Diabetes Care. No funding has been received for the production of this review.

References

1. Bode BW, Sabbah H, Davidson PC. What’s ahead in glucose monitoring? New techniques hold promise for improved ease and accuracy. Postgrad Med. 2001;109(4):44, 47–49.
2. Petrie JR, Peters AL, Bergenstal RM, et al. Improving the clinical value and utility of GGM systems: issues and recommendations. A joint statement of the European Association for the Study of Diabetes and the American Working Group. Diabetes Care. 2017;40:1614–1621.
3. Kulcu F, Tamada JA, Reach G, et al. Physiological differences between interstitial glucose and blood glucose measured in human subjects. Diabetes Care. 2003;26:2405–2409.
4. Siegmund T, Heinemann L, Kolassa R, et al. Discrepancies between blood glucose and interstitial glucose – technological artefacts or physiology: implications for selection of the appropriate therapeutic target. J Diabetes Sci Technol. 2011;5:766–772.
5. Pleus S, Schoemaker M, Morgenstern K, et al. Rate of change dependence of the performance of two CGM systems during induced glucose swings. J Diabetes Sci Technol. 2015;9:801–807.
6. Ji L, Guo X, Guo L, et al. A multicenter evaluation of the performance and usability of a novel glucose monitoring system in Chinese adults with diabetes. J Diabetes Sci Technol. 2017;11:290–295.
7. Kovatchev BP. Hypoglycemia reduction and accuracy of continuous glucose monitoring. Diabetes Technol Ther. 2015;17:330–333.
8. Kovatchev BP, Patek SD, Ortiz EA, et al. Assessing sensor accuracy for non-adjunct use of continuous glucose monitoring. Diabetes Technol Ther. 2015;17:177–186.
9. Bailey T, Bode BW, Christiansen MP, et al. The performance and usability of a factory calibrated flash glucose monitoring system. Diabetes Technol Ther. 2015;17:787–794.
10. Bonora B, Maran A, Ciclitri S, et al. Head-to-head comparison between flash and continuous glucose monitoring systems in outpatients with type 1 diabetes. J Endocrinol Inves. 2016;39:1391–1399.
11. Aberer F, Hajnsek M, Rumpler M, et al. Evaluation of subcutaneous glucose monitoring systems under routine environmental conditions in patients with type 1 diabetes. Diabetes Obes Metab. 2017;19:1051–1055.
12. Edge J, Acerini C, Campbell F, et al. An alternative sensor-based method for glucose monitoring in children and young people with diabetes. Arch Dis Child. 2017;102:543–549.
13. Scott E, Kautzky-Willer A. Accuracy evaluation of freestyle libre flash glucose monitoring system when used by pregnant women with diabetes. Diabetes Technol Ther. 2017;19(Suppl. 1):A84–A84.
14. Rodbard D. Continuous glucose monitoring: a review of successes, challenges, and opportunities. Diabetes Technol Ther. 2016;18:52–52–53.
15. Tamborlane WV, Beck RW, Bode BW, et al. Juvenile diabetes research foundation continuous glucose monitoring study group. continuous glucose monitoring and intensive treatment of type 1 diabetes. N Engl J Med. 2008;359:1464–1476.

16. Soupal J, Petruzela Kova, Flekac M, et al. Comparison of different treatment modalities for type 1 diabetes, including sensor-augmented insulin regimens, in 52 weeks of follow up: a COMOSAIR study. Diabetes Technol Ther. 2016;18:332–338.

17. Beck RW, Riddlesworth T, Ruedy K, et al. Effect of continuous glucose monitoring on glycemic control in adults with type 1 diabetes using insulin injections. The DIAMOND randomised trial. JAMA. 2017;317:371–378.

18. Lind M, Polonsky W, Hirsch I, et al. Continuous glucose monitoring vs conventional therapy for glycemic control in adults with type 1 diabetes treated with multiple daily insulin injections. The GOLD randomised clinical trial. JAMA. 2017;317:379–387.

19. Heinemann L, Freckmann G, Ehrmann D, et al. Real-time continuous glucose monitoring in adults with type 1 diabetes and impaired hypoglycaemia awareness or severe hypoglycaemia treated with multiple daily insulin injections (HypoDE): a multicentre, randomised controlled trial. Lancet. 2018. doi:10.1016/S0140-6736(18)30297-6.

20. Bolinder J, Antuna R, Geelhoed-Duijvestijn P, et al. Novel glucose-sensing technology and hypoglycemia in type 1 diabetes: a multicentre, non-masked, randomised controlled trial. Lancet. 2016;388:2254–2263.

21. Öskarsson P, Antuna R, Geelhoed-Duijvestijn P, et al. Impact of flash glucose monitoring on hypoglycaemia in adults with type 1 diabetes managed with multiple daily injection therapy: a pre-specified subgroup analysis of the IMPACT randomised controlled trial. Diabetologia. 2017. doi:10.1007/s00125-017-4527-5.

22. Dover AR, Stimson RH, Zammit NN. Gibb flash glucose monitoring improves outcomes in a type 1 diabetes clinic. J Diabetes Sci Technol. 2017;11:442–443.

23. Leelarahtha L, Wilmot EG. Flash forward: a review of flash glucose monitoring. Diabet Med. 2018;35:472–482.

24. Reddy M, Jugnee N, El Laboudi A, et al. A randomized controlled pilot study of continuous glucose monitoring and flash glucose monitoring in people with type 1 diabetes and impaired awareness of hypoglycemia. Diabetic Med. 2018. doi:10.1111/dme.13561.

25. Borot S, Benhamou PY, Atian C, et al. Practical implementation, education and interpretation guidelines for continuous glucose monitoring: a French position statement. Diabetes Metab. doi:10.1016/j.diabet.2017.10.009.

26. National Institute for Health and Care Excellence. FreeStyle Libre for monitoring. Available at: https://www.nice.org.uk/advice/mib110.

27. Freckmann G, Schluter S, Heinemann L, Diabetes technology working group of the German diabetes society. Replacement of blood glucose measurements by measurements with systems for real-time continuous glucose monitoring (rtCGM) or CGM With intermittent scanning (iscCGM): a German view. J Diabetes Sci Technol. 2017;11:653–656.

28. Donné T, Nimri R, Battelino T, et al. International consensus on use of continuous glucose monitoring. Diabetes Care. 2017;40:1631–1640.

29. Garg SK, Akturk HK. Flash glucose monitoring: the future is here. Diabetes Technol Ther. 2017;19:51–53.

30. Charleer S, Mathieu C, Nobels F, et al. Accuracy and precision of flash glucose monitoring sensors inserted into the abdomen and upper thigh compared to the upper arm (out of sight). Diabetes Obes Metab. 2018. doi:10.1111/dob.13239.

31. Standards of medical care in diabetes -2017. Summary of revisions. Diabetes Care. 2017;40(Suppl. 1):S4-S5.

32. Riddle M, Gerstein HC, Cefalu WT. Maturation of CGM and glycaemic measurements beyond HbA1c – a turning point in research and clinical decisions. Diabetes Care. 2017;40:1611–1613.

33. Wright LA-C, Hirsch I. Metrics beyond HbA1c in diabetes management: time in range, hypoglycaemia, and other parameters. Diabetes Technol Ther. 2017;19:5-16-5-26.

34. Ajan RA. How can we realize the clinical benefits of continuous glucose monitoring. Diabetes Technol Ther. 2017;19(Suppl. 2):S27–S36.

35. Cryer PE. Hypoglycaemia: the limiting factor in the glycaemic management of type I and type II diabetes. Diabetologia. 2002;45:937–948.

36. Gorst C, Kwok CS, Aslam S, et al. Long-term glycaemic variability and risk of adverse outcomes: a systematic review and meta-analysis. Diabetes Care. 2015;38:2354–2369.

37. Borges U Jnr, Kubiak T. Continuous glucose monitoring in type 1 diabetes: human factors and usage. J Diabetes Sci Technol. 2016;10:633–639.

38. Giani E, Snelgrove R, Volkening LK, et al. Continuous glucose monitoring (CGM) adherence in youth with type 1 diabetes: associations with biomedical and psychosocial variables. J Diabetes Sci Technol. 2017;11:476–483.

39. Kubiak T, Mann CG, Barnard KC, et al. Psychosocial aspects of continuous glucose monitoring: connecting to the patients’ experience. J Diabetes Sci Technol. 2016;10:859–863.

40. Vigersky R, Shrivastav M. Role of continuous glucose monitoring for type 2 in diabetes management and research. J Diabetes Complications. 2017;31:280–287.

41. Vigersky RA, Fonda SJ, Chellapa M, et al. Short- and long-term effects of real time continuous glucose monitoring in patients with type 2 diabetes. Diabetes Care. 2012;35:32–38.

42. Beck RW, Riddlesworth TD, Ruedy K, et al. Diamond study group continuous glucose monitoring versus usual care in patients with type 2 diabetes receiving multiple daily insulin injections. A randomised trial. Ann Int Med. 2017;167:365–374.

43. Haak T, Hanire H, Ajan R, et al. Flash glucose-sensing technology as a replacement for blood glucose monitoring for the management of insulin-treated type 2 diabetes: a multicenter, open-label randomized controlled trial. Diabetes Ther. 2017;8:55–73.

44. Allen NA, Fain JA, Braun B, et al. Continuous glucose monitoring counselling improves physical activity behaviours of individuals with type 2 diabetes: a randomised clinical trial. Diabetes Res Clin Pract. 2008;80:371–379.

45. Meade LT. The use of continuous glucose monitoring in patients with type 2 diabetes. Diabetes Technol Ther. 2012;14:190–195.

46. Bergenstal RM, Ahmann AJ, Baily T, et al. REcommnedations for standardising glucose reporting and analysis to optimize clinical decision making in diabetes: the ambulatory glucose profile. Diabetes Technol Ther. 2013;15:198–211.

Received: 01-05-2018 Accepted: 21-08-2018