https://doi.org/10.33591/sfp.50.6.u1

Unit No. 1

GLYCAEMIA BEYOND HBA1C: UNDERSTANDING THE LIMITATIONS OF HBA1C AND RATIONALISING THE USE OF CONTINUOUS GLUCOSE MONITORING TO OPTIMISE GLYCAEMIA IN TYPE 2 DIABETES

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ABSTRACT

Diabetes prevalence in Singapore is rising, with a large percentage of people with diabetes not achieving target haemoglobin A1c (HbA1c) levels. Monitoring of glucose levels is an integral part of diabetes management. Traditional methods like HbA1c and self-monitoring of blood glucose (SMBG) have limitations, especially in people with high glucose variability. Continuous glucose monitoring (CGM) technology has advanced considerably in the past few decades and provides real-time insights on glucose levels (overcoming the limitations of HbA1c), without the need for frequent finger pricking required for SMBG. CGM-derived metrics like time in range provide a comprehensive view of glycaemia, aiding in personalised management plans and reducing diabetes complications. CGM shows promise not only for type 1 diabetes, but also for type 2 diabetes management, improving HbA1c levels, reducing hypoglycaemia, and enhancing lifestyle modifications. In this review, the role of CGM in type 2 diabetes care is summarised.

Keywords: continuous glucose monitoring; glucose variability; glycaemia; time in range; type 2 diabetes

SFP2024; 50(6): 5-10

INTRODUCTION

The prevalence of type 2 diabetes (T2D) in adults in Singapore is expected to double from 7.3 percent in 1990 to 15 percent in 2050.[1] Moreover, in a health survey done in 2020 on adults with diabetes in Singapore, a quarter of the participants had suboptimal glycaemia, with haemoglobin A1c (HbA1c) >7 percent.[2]

Glucose monitoring is an integral part of diabetes care and aids in optimising glycaemia.[3,4] It facilitates optimisation of glucose-lowering therapy and may help in providing guidance on improving lifestyle for diabetes management.[3,4] However, there are challenges with glucose monitoring tools that are used routinely. The primary tools for measuring glucose levels, such as HbA1c and self-monitoring of blood glucose (SMBG), do not reveal a complete picture of glycaemia. SMBG is associated with limitations such as low user acceptability.[3,4] The advent of continuous glucose monitoring (CGM) has revolutionised glucose monitoring and facilitated proactive glucose management.[5,6] In this review article, we summarise the role of CGM in diabetes care.

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OVERVIEW OF GLUCOSE TESTING FOR DIABETES MANAGEMENT

HbA1c, a blood test for glycated haemoglobin, was discovered in 1969 and has emerged as one of the most important indicators of glycaemia in people with diabetes (PwD).[7] In 1980s, finger-prick testing of blood glucose or SMBG was introduced for self-monitoring of glucose; however, user acceptability is still an issue.[4,8] Glucose monitoring was further revolutionised with the approval of the first CGM device in 1999, which has undergone continuous advancements over the years, with professional and personal (real-time CGM [rtCGM] and intermittently scanned CGM [isCGM]) devices currently available for use.[6,8] Most CGM devices available today are factory-calibrated, which means that the user is not required to periodically do a finger prick for calibrations.[9]

PROBLEMS WITH HBA1C TESTING

Analytical

Haemoglobin A (HbA) is the most abundant form of haemoglobin in adults.[10] However, haemoglobin variants, such as HbS, HbE, HbC, and HbD, are found in approximately 7 percent of the world's population and affect the accuracy of certain HbA1c assays,[10,11] which can lead to inappropriate interpretation and clinical management.[10,12]

Biological

Biological variations, including genetic polymorphisms, differential glycation rates, and ethnicity[13,14] influence HbA1c levels, which may lead to discordance between HbA1c levels and the individual's overall glycaemia.[15,16] HbA1c may not be a reliable indicator of glycaemia in conditions where red blood cell (RBC) life span is altered, like in iron deficiency anaemia, or where RBC turnover is increased, such as in sickle cell disease and glucose-6-phosphate dehydrogenase (G6PD) deficiency.[3,17]

Mathematical

HbA1c is an indirect measure of average glycaemia over approximately three months and does not assess glycaemic variability or hypoglycaemia.[3] Hence, even when there are no analytical or biological issues present, a HbA1c can only at best provide an estimated average of a person's glycaemia,[3] without any information on the extent of hypoglycaemia and postprandial hyperglycaemia (glucose variability).

THE RISE OF CONTINUOUS GLUCOSE MONITORING

CGM overcomes the problems with HbA1c testing.

Analytical: In PwD with Hb variants that interfere with HbA1c assessments, CGM is a valuable tool to assess glycaemia and guide subsequent diabetes management.[11] An alternative is periodic SMBG.[18]

Biological: RBC biology does not affect glucose levels detected by the CGM sensor.[4]

Mathematical: CGMs generate sensor glucose levels every 5-15 minutes, corresponding to 96-288 readings per day.[19] The device also provides a wealth of valuable individual data regarding glycaemic variability, as well as time spent in hypo- or hyperglycaemia.[20]

ACCURACY OF CGM

CGM accuracy is measured using the percentage mean absolute relative difference (MARD) value, which is the percentage difference between the CGM sensor reading and a value measured at the same time using a reference method.[21,22] Over the years, CGM accuracy has improved such that the MARD value of the best CGMs is now in the range of 8-10 percent.[9,21,22] This is moving close to the MARD values for commercially available glucose meters, which range between 5.6-20.8 percent.[23]

CHALLENGES OF CGM

Analytical: Certain substances may interfere with glucose sensing by CGM sensors and result in spuriously high sensor glucose readings.[24,25] For example, Freestyle Libre users must be cautioned about possible interference from high dose vitamin C (>500 mg/day), and Dexcom G6 and Medtronic Guardian sensors may be affected by concomitant use of paracetamol or hydroxyurea.[24,25]

Biological: There is a lag time between blood and interstitial fluid glucose readings in physiology.[24,25] CGM systems try to overcome this using "lag compensation" in their algorithms.[26] Despite this, CGM systems may not be accurate during periods of rapid change in capillary glucose.[26] Hence, it is recommended that at times of rapid changes to glucose levels or when symptoms do not match the sensor glucose, CGM users should revert to SMBG.[27] For example, capillary glucose will respond quickly to treatment for an episode of hypoglycaemia, while sensor glucose may lag. Hence, PwD should not use a sensor glucose to assess recovery from hypoglycaemia.[27]

Mathematical: PwD and healthcare professionals may initially find the amount of data generated overwhelming; however, once a systematic stepwise approach to reviewing the CGM data is practised, especially with the use of time in range (TIR), CGM can become a useful tool in improving diabetes care.[3,28]

SUMMARY

CGM provides a complete glycaemic picture, without interference from RBC biology or haemoglobin variants.[4,11] Recent CGMs devices are factory-calibrated (eliminating the need for finger-prick testing and calibration) and have acceptable accuracy (MARD 8-10 percent).[9,21,22] Continued innovation in CGM devices may help resolve remaining issues such as the capillary-tissue glucose lag and sensor interference by medications and supplements.[24,25]

CGM METRICS

Dealing with CGM Data

As CGM becomes more widely used, CGM-derived metrics and targets have been standardised for consistent and effective reporting of outcomes.[29] Core CGM metrics, such as TIR, time above range (TAR), time below range (TBR), and glucose management indicator (GMI) provide a more comprehensive overview of glycaemia than HbA1c, facilitating more informed clinical decisions.[4]

Many clinicians are concerned about how to review and interpret the abundant CGM data, collected over days, in a short time in the clinic. Kong et al[29] and Szmuilowicz et al[30] have proposed a three-step approach to understanding what the problem is (reviewing CGM metrics to identify any hypoglycaemia, hyperglycaemia, or high glucose variability), where the problem is (reviewing the ambulatory glucose profile [AGP] report to identify the time period where the problem occurs), and identifying why it happens (reviewing daily glucose curves, e.g., studying the impact of overtreating an episode of hypoglycaemia by taking a large insulin dose when glucose was high) to guide treatment decisions.

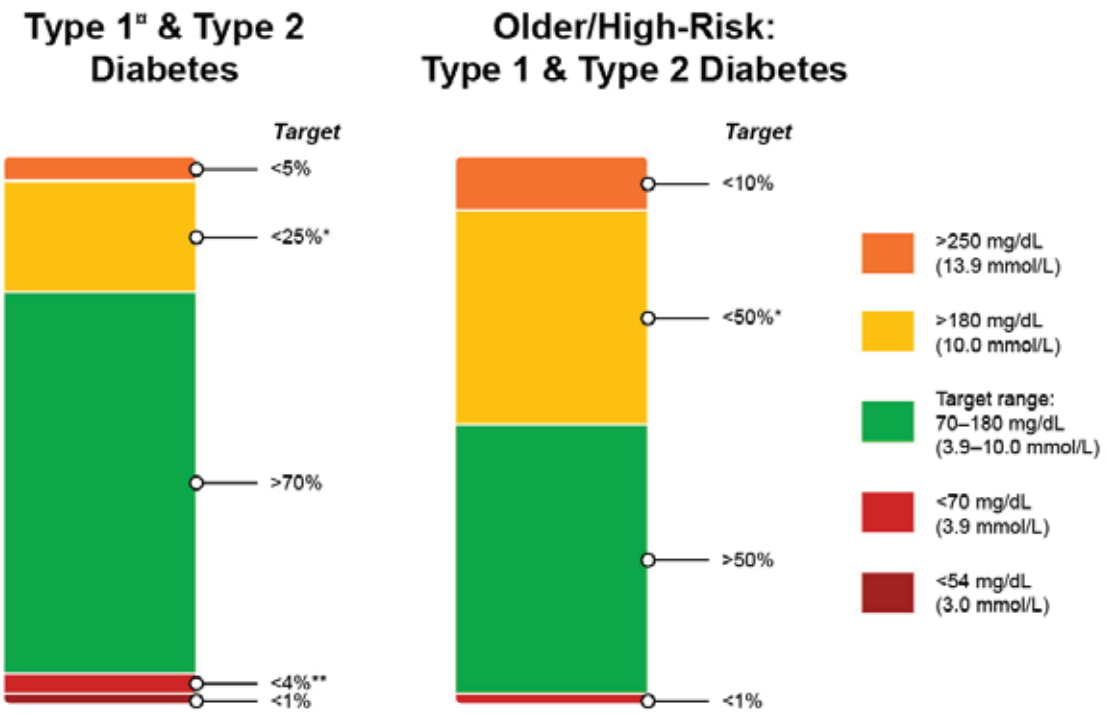
The Most Widely Used Metric: Time in Range

TIR refers to the time spent in the target glucose range (70-180 mg/dL or 3.9-10.0 mmol/L), with most guidelines targeting >70 percent of readings or time per day within range, while minimising time below range.[3,4,29,31] This corresponds to a HbA1c of approximately 7 percent.[32] TIR targets should be individualised according to user factors.[31] TIR is an intuitive and actionable metric at the individual level and provides insights for developing an individualised glycaemic management plan (refer to **Figure 1**).[3,5] A TIR-guided HbA1c lowering plan will minimise hypoglycaemia episodes and reduce glucose variability in PwD.[31]

Evidence for Time in Range

A higher TIR is associated with lower risk of microvascular complications in PwD, based on re-analysis of the landmark Diabetes Control and Complications Trial data.[33] Conversely, a lower TIR is associated with a higher risk of retinopathy and microalbuminuria.[33] Additionally, a 10 percent increase in TIR corresponds to a 0.8 percent (9 mmol/mol) decrease in HbA1c.[34]

Figure 1: International consensus recommendations for Time-in-Range



MANAGING GLUCOSE VARIABILITY WITH CGM

Background on Glucose Variability

Glucose variability is the fluctuation in glucose levels and is recognised as a clinically valuable marker of glycaemia.[4] High glucose variability is associated with an increased risk of hypoglycaemia and hyperglycaemia and predicts diabetic complications in PwD.[3,4,35] CGM uses standardised metrics and glucose data to quantify glycaemic variability, which cannot be evaluated with HbA1c or SMBG.[4] The preferred measure of glucose variability is the coefficient of variation (CV),[36] with a target of ≤36 percent recommended by most guidelines.[3,29,31]

Tackling Glucose Variability

Glucose variability commonly arises due to the mismatch between insulin/oral drug treatment and carbohydrate intake; matching the insulin or oral drug regimen with the intake of carbohydrates requires patient education on behavioural modifications, insulin timing and carbohydrate counting, and correction of insulin doses.[3,37,38] Moreover, PwD are often unaware of periods of high glycaemic variability, such as nocturnal hypoglycaemia.[39] Studies show that people with type 1 diabetes (T1D) had no subjective worsening of sleep quality at nights even with prolonged nocturnal hypoglycaemia (>150 minutes).[39] This suggests that people with diabetes may be unaware of prolonged nocturnal episodes of hypoglycaemia. Thus, monitoring with CGM is recommended in those at high risk of nocturnal hypoglycaemia. CGM could also make a PwD more aware of the impact of various dietary choices and exercise on their blood glucose.[40]

ROLE OF SELF-MONITORING OF BLOOD GLUCOSE

Self-monitoring of capillary glucose remains the mainstay of glucose monitoring among most people with type 2 diabetes (T2D).[4] Advantages of SMBG include wider availability and lower cost compared with CGMs.[4] On the other hand, SMBG needs finger pricking, which is painful and limits adherence.[4] In addition, it does not provide a detailed picture of glycaemia as it is limited to the times when a person is awake, thereby missing nocturnal glycaemic events.[4] Nonetheless, SMBG can provide valuable information and improve glycaemic control when it is structured.[4] A pre-meal blood glucose test is valuable in PwD on basal bolus insulin therapy, as this allows the person to judge the adequacy of a previous bolus insulin and increase or decrease the dose as necessary.[41] Post-meal glucose testing, while useful to assess the degree of postprandial hyperglycaemia, must be balanced against the risk of the person with diabetes taking additional insulin doses with the potential to cause insulin stacking and hypoglycaemia.[42]

The timing and structure of blood glucose testing should depend on the type of glucose-lowering medication used.[43] For instance, PwD on only basal insulin and oral drugs may be instructed to check fasting blood glucose and post-meal glucose to titrate the basal insulin dose to reduce the risk of hypoglycaemia. On the other hand, PwD on a basal bolus insulin regimen may need more frequent testing (e.g., pre-meals and bedtime).

BENEFITS OF USING CGM IN T2D

The benefits of using CGM for glucose monitoring in people with T1D is better understood than that for T2D. Nevertheless, recent evidence has highlighted the benefits for people with T2D as well. A randomised controlled trial comparing the efficacy of isCGM vs SMBG in 224 people with T2D on intensive insulin therapy demonstrated a reduction of time in hypoglycaemia (<70 mg/dL, <55 mg/dL, and <45 mg/dL) by 43 percent (p=0.0006), 53 percent (p=0.0014), and 64 percent (p=0.0013) for intervention participants vs control, but without a change of HbA1c at six months (adjusted mean ± standard error, -0.29±0.07 percent for isCGM group vs -0.31±0.09 percent for SMBG group, p=0.8222). Nocturnal hypoglycaemia was reduced by 54 percent (p=0.0001) in the isCGM group compared with the SMBG group. Glucose variability, measured as CV, reduced by 2.26±0.71 percent in the isCGM group compared with the SMBG group (p=0.0017). In addition, treatment satisfaction was higher in the isCGM group compared with the SMBG group (Diabetes Treatment Satisfaction Questionnaire [DTSQ], adjusted mean score ± standard error, 13.1±0.50 vs 9.0±0.72, p=0.001).[44]

The results of an open-label randomised controlled trial indicated that the use of isCGM in patients with T2D on multiple insulin injections may improve treatment satisfaction and significantly reduce HbA1c levels without increased risk of hypoglycaemia.[45] The change in HbA1c in the isCGM group vs the SMBG group was -0.82 percent vs -0.33 percent, respectively (p=0.005).

The results of another randomised trial demonstrated the benefit of rtCGM use in people with T2D who were not on prandial insulin, with HbA1c ≥7.0 percent but ≤12 percent. HbA1c at 12 weeks declined significantly in the rtCGM group vs SMBG group (mean ± standard deviation, 1.0%±1.1% vs 0.5%±0.8%, p=0.006). These results were achieved without an increase in in the number or dose of hypoglycaemic medications.[46]

The results of a prospective randomised trial in 57 people with T2D showed that rtCGM was also useful for PwD with poorly controlled T2D as a motivational device for modifying lifestyle patterns and could improve glycaemia when compared with SMBG.[47] The level of HbA1c at Week 12 in the rtCGM group significantly reduced compared with the SMBG group (mean ± standard deviation, 9.1±1.0% to 8.0±1.2% vs 8.7±0.7% to 8.3±1.1%, p=0.004). There was a significant reduction in body weight (p=0.014) and body mass index (p=0.008) in the rtCGM group compared to baseline, and a significant increase in total exercise time per week in the rtCGM group vs the SMBG group (p=0.02). Also, the glycaemic variability significantly decreased in the rtCGM group after two months of use (p=0.004), and there was an improvement in the proportion of TIR (80-250 mg/dL) for these PwD, although the difference was not statistically significant (p=0.07).

RATIONALISING THE USE OF CGM

The major limitation of using HbA1c or SMBG is the lack of a complete glycaemic picture, hence missing potential hypoglycaemia and postprandial hyperglycaemia when glucose variability is high.[3] Since glucose variability can only be determined using CGM,[3] it might be a challenge to identify PwD with high glucose variability in a clinical practice with limited access to CGM.[4,6]

Interestingly, a review of glucose variability across medication classes shows a clear progression from low to high glucose variability across medication classes of oral drugs without sulfonylureas (SUs), oral drugs such as SUs, basal-bolus insulins, and premixed insulins.[48-51] People on premixed insulin have higher glucose variability than basal bolus insulin.[52] The glucose variability is lowest in people on oral glucose-lowering medications without insulin and SU.[48,49] This information can be used in clinical practice to identify PwD who are at risk of high glucose variability. The data suggest that an HbA1c of 7 percent portrays a higher probability of hypoglycaemia and hyperglycaemia (glucose variability) in PwD on premixed insulin therapy,[52] compared with those on oral, non-SU drugs without insulin who have low glucose variability.[48] Thus, it is possible for healthcare providers to predict the likelihood of high glucose variability based on the type of medication used to treat diabetes. Other factors that increase the risk of hypoglycaemia include elderly age group[29] and a high degree of physical activity without making necessary modifications to glucose-lowering medications.[53,54]

Awareness of these factors will help the clinician make an informed decision regarding the use of CGM among people with T2D to improve their glycaemia.

CONCLUSION

Clinicians should be aware of the limitations of using HbA1c as the sole basis for assessing glycaemia, with special considerations for conditions that affect RBC turnover or haemoglobin variants.[3] In PwD with low glucose variability, diabetes management may be based on HbA1c targets alone. However, in PwD with likelihood of high glucose variability, structured SMBG or a CGM-based and TIR-guided management plan should be used to improve glycaemia.

FUNDING AND ACKNOWLEDGEMENTS

Funding for the development of this article was provided by Abbott Diabetes Care, Singapore. Medical writing support was provided by Radhika Das Chakraborty, PhD, and Ehsan Kachooei, PhD, of Nucleus Global, in accordance with Good Publication Practice 2022 guidelines (https://www.ismpp.org/gpp–2022).

CONFLICTS OF INTEREST

Dr Suresh Rama Chandran has received speaker fees from Abbott, Medtronic, Dexcom, AstraZeneca, Boehringer Ingelheim, Sanofi, and Roche Diabetes Care. He has also participated in advisory board meetings for Dexcom and Medtronic.

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LEARNING POINTS

- **CGM overcomes the challenges with other glucose measurement methods, such as HbA1c monitoring and SMBG, and the metrics associated with CGM (particularly TIR) provide a clear overview of the burden of hyperglycaemia and hypoglycaemia.**
- **CGM enables detection of postprandial hyperglycaemia and nocturnal hypoglycaemia (glucose variability) that are not detected by HbA1c and often missed with SMBG.**
- **The type of glucose-lowering medications in use predicts the risk of high glucose variability in PwD.**
- **CGM should be considered in PwD with high glucose variability or when nocturnal hypoglycaemia is suspected.**