A Review on Continuous Glucose Monitoring in Diabetes management

Jasmine Fathima[1], Anudeepa J[2], Pooja Muralidharan[3], Devanadhan[3], Bakkiyaselvan V[3], Balaji P[3]

{jas123fath@gmail.com[1], anudeeparagav@gmail.com[2], poojamuralidharandurgaram7890@gmail.com[3]}

Affiliation: Department of Pharmacy Practice, PSG College of Pharmacy[1] Department of Pharmaceutical Chemistry, PSG College of Pharmacy [2] PSG College of Pharmacy[3]

Abstract. In the last two decades, the global prevalence diabetes has increased significantly, leading to various chronic complications and heightened morbidity and mortality. Regular assess ment of glycemic control is crucial in diabetes management. Common techniques include self-monitoring of blood glucose and measurement of hemoglobin A1c. While SMBG helps evaluate therapy response, it has limitations such as providing singular measurements and dependency on patient adherence. HbA1c, reflecting average glucose levels, is a gold standard, but it doesn't capture glycemic fluctuations and can be unreliable in certain health conditions. Continuous glucose monitoring has become a valuable tool, offering insights into glycemic trends, time spent within the target range, and hypoglycemia. CGM data, despite a time lag with traditional blood glucose readings, provides comprehensive understanding over a 10–14-day period. CGMPs provide valuable insights into glycemic excursions and potentially hazardous fluctuations that might be overlooked with traditional SMBG.

Keywords: Continuous Glucose monitoring, Diabetes, Glycemic index, HbA1c, glycemic control..

1. Introduction

The global occurrence and frequency of type 1 and type 2 diabetes mellitus (DM) have significantly surged over the last several decades and are projected to persist rising. Diabetes is linked with numerous persistent complications leading to heightened morbidity and mortality. Therefore, alongside appropriate medical management, regular assessment of glycemic control is imperative for individuals with diabetes. Monitoring of glycemic status is considered a fundamental aspect of diabetes care, offering insights into the effectiveness of therapy and guiding lifestyle adjustments and medication regimens. Primary techniques for assessing glycemic Control measures include patient self-monitoring of blood glucose (SMBG) and hemoglobin A1c (HbA1c) assessment.

SMBG, for instance, can aid in evaluating an individual's response to therapy and has been shown to lessen HbA1c levels by 0.25–0.3%. However, it has limitations; providing only a singular "point-in-time" measurement, it does not offer information on the administration or rate of change of

ICSETPSD 2023, November 17-18, Coimbatore, India

DOI 10.4108/eai.17-11-2023.2342847

glucose levels. Additionally, its effectiveness is reliant on the patient's compliance to self-management, potentially leading to under-detection of nocturnal or asymptomatic hypoglycemia.

Haemoglobin A1c (HbA1c) serves as a biomarker indicating the glycated haemoglobin percentage in the blood, representing the average plasma glucose level over 8–12 weeks. Widely used for diabetes diagnosis and management, it is considered a gold common for assessing diabetes-related outcomes. Although HbA1c is cost-effective and easy to manage, it has limitations. It does not account for glycemic excursions, which have been linked to microvascular and macrovascular complications. Additionally, it may be undependable in certain health conditions such as anaemia,ss hemoglobinopathies, liver disease, and iron deficiency.[2]

Continuous glucose monitoring (CGM) has proven to be a valuable tool for evaluating treatment efficacy and safety in both type 1 and type 2 diabetes. It gives insights into time spent within the glycemic desired range and hypoglycaemia [1].

The glucose management indicator (GMI) aids in decision-making when actual and estimated HbA1c values differ, presuming a more personalized approach to treatment. GV, which reflects fluctuations in blood glucose levels over hours or days, plays a role in diabetes-related complications and poses a challenge in glycemic optimization. Various factors, including lifestyle, diet, comorbidities, and diabetes treatment, contribute to GV in patients. Control GV is crucial as it is linked to the frequency, duration, and severity of hypoglycemic events.

2. Continuos Glucose Monitoring (CGM)

Continuous glucose monitoring (CGM) traces interstitial glucose levels, providing a comprehensive understanding of glucose trends over a 10–14 day period, which can serve as an estimate for a 3-month period. Real-time CGM (rtCGM) data offers insights into how blood glucose levels are affected by meals, stress, and exercise, demonstrating its precision in diabetes management. However, CGM results do not at all times align with traditional finger stick blood glucose readings due to a time lag of roughly 15 minutes between interstitial and blood glucose measurements.

The ability to utilize CGM data without frequent capillary blood glucose (CBG) checks has revolutionized T1D management.[9][11].

CGM systems are categorized into intermittently viewed CGM (iCGM), commercially known as flash glucose monitoring (FGM), and real-time CGM, each providing distinct approaches to glucose monitoring. While the use of, CGM as a biomarker for blood glucose levels has certain limitations recent declarations from the research community highlight the limitations of HbA1c in accurately reflecting individual glucose patterns. In response, efforts have been made to embody elucidated clinically relevant outcomes beyond HbA1c in type 1 diabetes research, including outcomes such as hypoglycemia, hyperglycemia, time in glycemia span, diabetic ketoacidosis, and patient-reported end results. CGM profiles not only provide mean glucose concentration but also offer valuable insights into glycemic excursions, revealing potentially hazardous fluctuations in glucose levels that may be missed with traditional self-tracking of blood glucose (SMBG).

2.1 Advantages

Continuous glucose monitoring (CGM) offers comprehensive insights into glucose monitoring, revealing glycemic variability (GV), rate of change over time, and time allotted in hypo and hyperglycemia, which are not attainable through self-monitoring of blood glucose (SMBG). It is particularly beneficial for patients with severe or nocturnal hypoglycemia, especially those with hypoglycemia lack of awareness.

The Diabetes Control and Complications Trial (DCCT) has exhibited the benefits of intensive glycemic control in reducing the risk of complications in type 1 diabetes mellitus patients [10]

Continuous Glucose Monitoring (CGM) devices provide real-time or near real-time measurements of blood glucose levels in the subcutaneous tissue. These systems offer several advantages, including the display of directional arrows indicating the rate of glucose change, alarms for low and high blood glucose levels, and data storage for later review, enabling the detection of glucose trends and aiding in the improvement of glycemic control. The frequent glucose measurements offered by CGM systems allow for better assessment of fasting and after lunch the blood glucose levels, adjustment of insulin doses, understanding the impact of exercise on glucose levels, and identification of acknowledgement hypoglycemia, particularly in the event of hypoglycemia lack of awareness or prolonged hyperglycemia.

Additionally, the data obtained from CGM devices can be transmitted to healthcare professionals via internet systems, facilitating convenient treatment adjustments and serving as a valuable tool for patient education to enhance their understanding of blood glucose fluctuations. CGM can also complement insulin pump treatment, with the potential to even allow for the discontinuation of the pump in cases where sensor alarms do not elicit a response. Moreover, the utilization of CGM has the added benefit of potentially cutdown the frequency of capillary glucose measurements [15].

Trials made of DIAMONDS and GOLD have demonstrated that CGM leads to improved glycemic control in patients with type 1 diabetes mellitus (DM) treated with multiple daily insulin shots as treatment. Similarly, in type 2 DM, CGM has been shown to improve mean amplitude of glycemic excursion (MAGE) and improve glycemic control. Recent meta-analyses have indicated that CGM can effectively reduce HbA1c levels and time spent in hypoglycemia in type 2 DM patients. Additionally, CGM data can serve as a noteworthy educational instrument for patients.

2.2 Disadvantages

Despite its advantages, CGM faces limitations such as reimbursement issues, the need for periodic sensor replacement in long-duration implantable CGM devices, and a lack of established clinical guidelines for its role in managing type 2 DM.

Continuous Glucose Monitoring Systems (CGMS) offer numerous advantages, but their accuracy remains a significant concern due to discrepancies between the CGMS and capillary blood glucose measurements. This divergence can lead to erroneous decisions during rapid changes in blood glucose levels. Studies have reported varying levels of inaccuracy, with some revealing differences of up to 21% between plasma and subcutaneous glucose values. Error Grid Analysis has shown challenges in interpreting sensor data in clinical practice, with a substantial proportion of data falling outside acceptable accuracy zones. Various evaluations of Medtronic RT-CGM sensor accuracy have also indicated mixed results, with different levels of accuracy observed across different glucose ranges.

The motif of blood glucose change is considered more informative than absolute values from the sensor. FDA recommendations emphasize that the CGMS provides approximate, rather than precise, data on blood glucose levels, and readings should be confirmed by capillary glucose measurements for medical assistance. Monitoring the interstitial signal (ISIG) can help identify sensor performance issues. Calibration data entry timing significantly impacts accuracy, and the calibration process needs to be adjusted to minimize the impact of false sensor operation.

The issue of false alarms also poses a challenge, with alarm settings impacting detection rates and false alarms. Skin reactions, local infections, and scarring after sensor removal are additional concerns associated with CGMS use. Patient education is crucial for proper sensor use, and experience over time can improve performance. Adolescents may have specific considerations, with the size of the sensor being a factor in the decision to initiate or continue CGMS use [15].

However, recent technological advancements and evidence from the literature are addressing these issues. The emergence of anticipated that the development of closed loop insulin delivery systems and a new generation of insulin pumps with automated suspension of insulin infusion in response to hypoglycemia will greatly improve the therapeutic usability and impact of CGM.

2.3 Impact of CGM on diabetic profile

Although HbA1c is the current gold standard for evaluation glycemic control, it only provides an average measure of glycemic status over a few months and does not address glucose variability and hypoglycemia [12].

To personalize treatment decisions effectively, healthcare providers should standardize and utilize glycemic data to enhance effectiveness and security for patients. CGM metrics offer a more individualized approach to diabetes management and help overcome the limitations of HbA1c. They detect within-day and day-to-day glucose variability, time spent in the glycemic target range, and time spent in hypoglycemia, thereby improving patient self-management. The supervisory of glucose variability is possibility linked to the frequency, duration, and severity of hypoglycemic events and may impact the pathogenesis of diabetes problems and the quality of life of the patient.

Studies have shown that the use of continuous glucose monitoring (CGM) can lead to a notable decrease in the duration of time spent in both moderate and critical hypoglycemia ranges while increasing the time spent within the target range (70-180 mg/dL). Additionally, the impact of sensor-augmented pump (SAP) therapy on metabolic control has been widely evaluated. SAP therapy has been found to effectively reduce mean A1c levels in both adult and pediatric patients. Notably, in patients using multiple daily injections (MDI), switching to SAP therapy helped lower A1c levels to the same extent as those originally assigned to the SAP arm of the study. Despite some conflicting results, SAP therapy has generally been to correlated with less time spent when hypogycemic in contrast to continuous subcutaneous insulin infusion (CSII).

In a recent systematic review and meta-analysis, CGM was found to modestly reduce HbA1c levels by 0.17% and increase time spent in the target range by 70.74 minutes. (1). It also effectively reduced time below range (TBR), time above range (TAR), and coefficient of variation (CV), indicating improved glucose variability [13].

Participants using CGM reported high satisfaction levels, increased time within the target glucose range (70-180 mg/dL), decreased time with low glucose concentrations, and reduced glycemic variability [4].

Few studies revealed that continuous glucose monitoring (CGM) leads to significant improvements in diabetes-specific quality of life (QOL) especially methods to learn discomfort associated with diabetes and boost the trust in hypogycemia in people with type 1 diabetes (T1D) using multiple daily insulin (MDI) injections, in comparison to those who use self-monitoring of blood glucose (SMBG) only [5].

Studies have shown that increased sensor usage, rather than the use of pumps alone, is associated with a greater reduction in A1C, highlighting the positive impact of CGM on glycemic control [16].

Real-time CGM use has been linked to more intensive manipulation of insulin delivery, including adjustments in dosages, timing, and treatment responses to alerts. Experienced CGM users have reported modifying their insulin doses, adjusting insulin timing, proactively addressing potential hypoglycemia, and lowering individualized glucose targets after initiating CGM [8]

The use of CGM in diabetes management has shown consistent benefits, including faster time within the desired glucose range and a reduction in hypoglycemic events [6][7].

The use of continuous glucose monitoring (CGM) is essential in clinical trials for new diabetes treatments, as it provides robust and valuable data [14].

2.4 CGM in market

The development of continuous glucose monitoring (CGM) systems has evolved significantly since the introduction of the first prototypes in 1999. Initial systems, such as the Medtronic Real-Time Guardian, Dexcom SEVEN Plus, and Abbott Freestyle Navigator, had limitations in accuracy, with Mean Absolute Relative Difference (MARD) values ranging from 12.8% to 16.7%, higher than those of self-monitoring of blood glucose (SMBG). These limitations hindered their early adoption by users and healthcare professionals.

There are currently several Continuous Glucose Monitoring (CGM) systems accepted by the FDA and CE mark. These include the Guardian Real-Time by Minimed Medtronic, the Freestyle pathfinder by Abbott Diabetes Care, and the DexCom SEVEN Plus by DexCom. The Guardian Real-Time and DexCom SEVEN Plus are 7-day sensors that require 2-4 adjustment per day, putting on show glucose values every 5 minutes. The Freestyle Navigator, on the other hand, is a 5-day sensor that displays glucose values every 10 minutes, with 4 calibrations required over the 5-day period. The DexCom SEVEN Plus is approved for patients over 18 years old.

Additionally, the Medtronic iPro2 has recently entered the market as a professional CGM device, allowing data collection in a blinded manner for the evaluation of patient treatment. Unlike other systems, the iPro2 does not require calibration during its use, as calibration data are entered in retrospect, eliminating patient interaction bias. It stores and provides data for review by healthcare professionals and patients, including a list of glucose measurements, meal times, and exercise information. The Medtronic iPro2 claims better accuracy with a mean absolute relative difference (MARD) of 11% compared to the defender RT's 15.8%.

The CGM systems mentioned above utilize an electroenzymatic sensor. Another CGM system based on the microdialysis method, known as GlucoDay by A. Menarini Diagnostics, is also approved for use in the US and Europe. GlucoDay is a 48-hour sensor that requires 2 calibrations per day and allows data storage for retrospective analysis.

3. Future perspectives

The advancements in technology for managing diabetes emphasizes the positive impact of continuous subcutaneous insulin infusion (CSII), continuous glucose monitoring (CGM) systems, and sensor-enhanced insulin pumps on glycemic control and quality of life. Despite these advancements, many patients struggle to achieve recommended glycemic goals, indicating the need for further research and solutions [3].

The combination of CGM data with data from insulin pumps and wearable sensors will allow for the improvement of algorithms for glucose prediction and automatic basal insulin modulation, potentially enhancing the management of diabetes. Integrating CGM data with other clinical data sources, such as registry of clinical conditions, electronic health records, prescription registries, and laboratory tests, will provide important clinical context to CGM data. This integrated approach could lead to the generation of a comprehensive digital diabetes data ecosystem , enabling the extraction of fresh perspedires into the mechanisms of diabetes progression and the development of personalized data analytics for diabetes management and the prevention of related complications.

References

[1] Chehregosha, H., Khamseh, M. E., Malek, M., Hosseinpanah, F., & Ismail-Beigi, F. (2019). A view beyond HBA1C: Role of Continuous glucose Monitoring. *Diabetes Therapy*, *10*(3), 853–863. https://doi.org/10.1007/s13300-019-0619-1

[2] Maiorino, M. I., Signoriello, S., Di Maio, A., Chiodini, P., Bellastella, G., Scappaticcio, L., Longo, M., Giugliano, D., & Esposito, K. (2020). Effects of continuous glucose monitoring on metrics of glycemic control in diabetes: A systematic review with meta-analysis of randomized controlled trials. *Diabetes Care*, *43*(5), 1146–1156. https://doi.org/10.2337/dc19-1459

[3] Hommel, E., Olsen, B. S., Battelino, T., Conget, I., Schütz-Fuhrmann, I., Hoogma, R. P., Schierloh, U., Sulli, N., Gough, H., Castañeda, J., De Portu, S., & Bolinder, J. (2014). Impact of continuous glucose monitoring on quality of life, treatment satisfaction, and use of medical care resources: analyses from the SWITCH study. *Acta Diabetologica*, *51*(5), 845–851. https://doi.org/10.1007/s00592-014-0598-7

[4] Aleppo, G., Ruedy, K. J., Riddlesworth, T. D., Kruger, D. F., Peters, A. L., Hirsch, I. B., Bergenstal, R. M., Toschi, E., Ahmann, A. J., Shah, V. N., Rickels, M. R., Bode, B. W., Philis-Tsimikas, A., Pop-Busui, R., Rodriguez, H., Eyth, E., Bhargava, A., Kollman, C., & Beck, R. W. (2017). REPLACE-BG: a randomized trial comparing continuous glucose monitoring with and without routine blood glucose monitoring in adults with Well-Controlled Type 1 Diabetes. *Diabetes Care*, *40*(4), 538–545. https://doi.org/10.2337/dc16-2482

[5] Cooke, D., Hurel, S. J., Casbard, A., Steed, L., Walker, S., Meredith, S., Nunn, A., Manca, A., Sculpher, M., Barnard, M., Kerr, D., Weaver, J. B., Ahlquist, J., & Newman, S. (2009). Randomized controlled trial to assess the impact of continuous glucose monitoring on HbA1cin insulin-treated diabetes (MITRE Study). *Diabetic Medicine*, *26*(5), 540–547. https://doi.org/10.1111/j.1464-5491.2009.02723.x

[6] Danne, T., Nimri, R., Battelino, T., Bergenstal, R. M., Close, K. L., DeVries, J. H., Garg, S. K., Heinemann, L., Hirsch, I. B., Amiel, S. A., Beck, R. W., Bosi, E., Buckingham, B. A., Cobelli, C., Dassau, E., Doyle, F. J., Heller, S., Hovorka, R., Jia, W., . . . Phillip, M. (2017). International Consensus on use of Continuous Glucose Monitoring. *Diabetes Care*, *40*(12), 1631–1640. https://doi.org/10.2337/dc17-1600

[7] Huang, E. S., O'Grady, M. J., Basu, A., Winn, A. N., John, P. M., Lee, J., Meltzer, D. O., Kollman, C., Laffel, L. M., Tamborlane, W. V., Weinzimer, S. A., & Wysocki, T. (2010). The Cost-Effectiveness of continuous glucose monitoring in Type 1 diabetes. *Diabetes Care*, *33*(6), 1269–1274. https://doi.org/10.2337/dc09-2042

[9] Beck, R. W., Riddlesworth, T. D., Ruedy, K. J., Ahmann, A. J., Bergenstal, R. M., Haller, S., Kollman, C., Kruger, D. F., McGill, J. B., Polonsky, W. H., Toschi, E., Wolpert, H., & Price, D. A. (2017). Effect of continuous glucose monitoring on glycemic control in adults with Type 1 diabetes using insulin injections. *JAMA*, *317*(4), 371. https://doi.org/10.1001/jama.2016.19975

[10] Polonsky, W. H., Hessler, D., Ruedy, K. J., & Beck, R. W. (2017). The impact of continuous glucose monitoring on markers of quality of life in adults with Type 1 diabetes: Further findings from the DIAMOND randomized clinical trial. *Diabetes Care*, *40*(6), 736–741. https://doi.org/10.2337/dc17-0133

[11] Castle, J. R., & Jacobs, P. G. (2016). Nonadjunctive use of continuous glucose monitoring for diabetes treatment decisions. *Journal of Diabetes Science and Technology*, *10*(5), 1169–1173. https://doi.org/10.1177/1932296816631569

[12] Cappon, G., Vettoretti, M., Sparacino, G., & Facchinetti, A. (2019). Continuous Glucose Monitoring Sensors for Diabetes Management: A Review of Technologies and Applications. *Diabetes & Metabolism Journal*, *43*(4), 383. https://doi.org/10.4093/dmj.2019.0121

[13] McAndrew, L. M., Schneider, S. H., Burns, E., & Leventhal, H. (2007). Does patient blood glucose monitoring improve diabetes control? *The Diabetes Educator*, *33*(6), 991–1011. https://doi.org/10.1177/0145721707309807

[14] Dicembrini, I., Mannucci, E., Monami, M., & Pala, L. (2019). Impact of technology on glycaemic control in type 2 diabetes: A meta-analysis of randomized trials on continuous glucose monitoring and continuous subcutaneous insulin infusion. *Diabetes, Obesity and Metabolism*, *21*(12), 2619–2625. https://doi.org/10.1111/dom.13845

[15] Danne, T., Nimri, R., Battelino, T., Bergenstal, R. M., Close, K. L., DeVries, J. H., Garg, S. K., Heinemann, L., Hirsch, I. B., Amiel, S. A., Beck, R. W., Bosi, E., Buckingham, B. A., Cobelli, C., Dassau, E., Doyle, F. J., Heller, S., Hovorka, R., Jia, W., . . . Phillip, M. (2017b). International Consensus on use of Continuous Glucose Monitoring. *Diabetes Care*, *40*(12), 1631–1640. https://doi.org/10.2337/dc17-1600

[16] Giani E, Scaramuzza AE, Zuccotti GV. Impact of new technologies on diabetes care. World J Diabetes. 2015 Jul 25;6(8):999-1004. doi: 10.4239/wjd.v6.i8.999. PMID: 26240696; PMCID: PMC4515449.