Title:

CGM Impact and Implications of Real-World Evidence: Past, Present, and Future

Running Title:

CGM Real-World Evidence

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(ABSTRACT)

Randomized controlled trials (RCTs), which are are considered the highest level of scientific evident, have shown significant glycemic benefits associated with use of continuous glucose monitoring (CGM) in individuals with diabetes who are treated with intensive insulin regimens. However, numerous prospective, retrospective, and observational studies have investigated the impact of CGM in various diabetes populations treated witn non-intensive therapies. Results from these studies have contributed to changes in payer coverage, prescriber behaviors and expanding use of CGM. This article reviews findings from recent real-world studies, highlight the key lessons learned from these studies, and discuss how we need to move forward in increasing utilization of and access to CGM among all diabetes patients who would benefit from this technology.

Introduction

Early, effective and sustained glycaemic control is fundamental to the management of all types of diabetes mellitus, and patient glucose measurement with continuous glucose monitoring (CGM) is the most informative approach. There is growing interest in using real-world evidence in conjunction with randomized controlled trials (RCTs) to assess the patient utilization, clinical outcomes, and patient attitudes toward use of CGM in real-world settings. Today, an increasing number of regulatory agencies and payers now require pharmaceutical and medical device manufactuers to submit findings from real-world studies in addition to RCTs when assessing the safety, effectiveness and cost-benefit parameters of new medications and medical devices.[1-4]

During the past five years, numerous prospective, retrospective, and observational studies have investigated the impact of CGM in various diabetes populations. Results from these studies have contributed to notable changes in payer coverage, prescriber behaviors and expanding use of CGM. In this article, we review findings from recent real-world studies, highlight the key lessons learned from these studies, and discuss how we need to move forward in increasing utilization of and access to CGM among all diabetes patients who would benefit from this technology.

Randomized Controlled Trials vs. Real-World Evidence

Randomized controlled trials (RCTs) are considered the highest level of scientific evidence when investigating the efficacy of a given intervention and in developing clinical practice guidelines. However, RCTs do not provide critical information about the effectiveness of an intervention when used in uncontrolled, or usual care clinical settings. This is particularly important when the invention involves use of a diabetes technology, the efficacy of which is dependent on user behavior.

For example, in diabetes pharmaceutical RCTs, subjects receive a medication and investigators assess whether and/or to what degree it lowers HbA1c compared to a control group. In RTCs involving CGM, the assessment is more complex because it involves device performance and both user and clinician behaviors. This raises several questions. Did the study participants wear their sensor as prescribed? Did they review their data frequently? Did they respond appropriately to their data? Did their clinicians download and accurately interpret the data? Did providers review the data with participants and collaborate using shared decision-making regarding therapy adjustments? Unfortunately, the answers are often not reported or simply unknown. This array of ambiguities leaves unanswered the question of whether and/or how effective the use of CGM devices will be under conditions of usual care.

Indeed, when findings from RCTs are positive, we generally infer that the answers to these questions were affirmative; namely, the CGM sensor functioned properly and both study participants and their healthcare providers were successful in optimizing its clinical impact. However, a major limitation of RCTs is that they do not provide insights into the effectiveness of CGM use by patients in the absence of such structured supervision and follow up over the course of their everyday lives.

Timely and comprehensive real-world evidence (RWE) fills this vital information gap. An acknowledged shortcoming of RWE is that demographic characteristics and specifics about how patients use their CGM devices and glucose data often remain somewhat ill-defined. However, we can generally assume that the patients received varying levels of education and support from their healthcare providers and were able to use their glucose data with varying levels of appropriateness and expertise to drive improved diabetes outcomes. Accordingly, overall trends have revealed achievement of measurable clinical benefit from CGM use across a broad spectrum of clinical scenarios. When findings from real-world studies and RCTs are considered in aggregate, a clearer picture emerges about the performance of CGM devices, the ideal conditions under which CGM use is optimized, and an understanding that CGM can improve glycemic control even if/when its use is not fully optimized in large diabetes populations.

Limitations of Current Glucose Monitoring Methods

HbA1c

Glycated hemoglobin (HbA1c) remains the gold standard for assessing long-term glycemic control. However, it does not provide information about the frequency or magnitude of inter- and intra-day glucose excursions. This real-time information is necessary for accurate patient assessment and appropriate therapeutic decision-making in clinical practice. Moreover, the accuracy of the HbA1c measurement can be falsely elevated or decreased in individuals with chronic kidney disease,[5] anemia,[6] and hemoglobinopathies.[7] Studies have also shown that test results can be influenced by pregnancy[8] and ethnic/racial differences in glycation rates.[9-11]

Blood Glucose Testing

Although traditional blood glucose monitoring (BGM) provides point-in-time measurements of current glucose levels, testing must be frequent in order for the data to be actionable. Moreover, BGM users are burdened by painful fingersticks, inconvenience of carrying testing materials, interruption of daily activities, and difficulty interpreting their data, often resulting in non-adherence with prescribed testing.[12-15] For example, Siddiqui et al. recently reported that 61.9% of 33 type 2 diabetes (T2D) adults who were treated with anti-hyperglycemic oral medications, reported that they did not use BGM in their daily regimen.[15]

Overview of CGM and Metrics for Clinical Use

CGM Systems

CGM overcomes several limitations of current monitoring methods. The most current CGM systems automatically transmit a constant stream of data to the user's handheld reader or smartphone. Thus, users do not have to interrupt their daily activities to obtain and view their glucose data. Moreover, users can easily interpret their data, which are presented in standardized numerical and graphical formats. By simply looking at their reader or smartphone, users can see their current glucose level, recent trends, and rate-of-change arrows that indicate the direction and velocity of changing glucose. These systems feature programmable alerts that warn users of current or impending severe glycemic events. As an additional safeguard, current CGM systems allow users to share their glucose data in real time with family members, friends, and caregivers, who can provide emergency assistance when needed.

CGM Metrics and Data Download Software

In 2019 an expert panel published targets for key CGM metrics for use in clinical practice,[16] which were subsequently endorsed by many medical organizations.[17-20] The metrics include average glucose, glycemic variability (reported as standard deviation [SD] and percentage coefficient of variation [%CV]), percentage of time in range (%TIR 70-180%), time below range (%TBR <70 mg/dL, <54 mg/dL), time above range (%TAR >180 mg/dL, >250 mg/dL), and Glucose Management Indicator (GMI), which is a leading indicator of HbA1c.

To facilitate interpretation of these metrics, the International Diabetes Center (Minneapolis, MN) developed the Ambulatory Glucose Profile (AGP) software that automatically calculates and displays these metrics in easy-to-understand formats along with the goal for each metric.[21] (**Figure 1**) Many CGM companies have integrated the AGP Report into their own download software.

The Recent Past

Evidence Supporting CGM Use with Non-Intensive Therapies

Several real-world studies have shown significant improvements in HbA1c along with reductions in frequency and severity of hypoglycemia events in individuals treated with intensive insulin regimen.[22-27] Recent real-world studies have also shown similar glycemic benefits among individuals treated with basal insulin only and non-insulin therapies.[28-36]

As reported by Wright et al. in a large database analysis, six months of CGM resulted in significant HbA1c reductions (from 10.1% to 8.6%, p<0.001) in a retrospective database analysis of 1,034 adults with non-intensively treated T2D adults.[28] Significant glycemic improvements have also been reported in similar U.S. and Canadian retrospective studies.[30, 31] Findings of decreased rates of adverse drug events (ADEs) and all-cause hospitalizations (ACHs) have also been reported by Miller et al. in a large cohort (n=10,282) of T2D adults treated with non-intensive or non-insulin therapy.[29]

In a 6-month, prospective, interventional, single-arm study, Grace et al. investigated the impact of CGM use in 38 T2D adults (58% treated with non-insulin medications). At study end the mean HbA1c level decreased from 10.1% at baseline to 7.3% ($p<0.001$), with significant increases in %TIR ($p<0.001$) and significant reductions in body weight ($p=0.002$).[32]

Importantly, many real-world studies showed significant associations between CGM use and improvements in quality of life, including increased treatment satisfaction,[22, 37] enhanced sense of wellbeing,[37] less hypoglycemia fear,[27, 37] and improvements in other health-related measures.[22, 24, 26, 37, 38]

Evidence Supporting CGM Metrics

When the CGM metrics were established, there were some concerns that there was little evidence to link some of these metrics, specifically, %TIR, %TBR, and %TAR, to diabetes complications.[39] However, RWE now demonstrates the strength of this association. For example, in a recent study by Kim et al., investigators assessed the association between cardiovascular autonomic neuropathy (CAN) and CGM metrics, comparing 84 T2D adults with known CAN with those without CAN in an outpatient setting, using blinded CGM data.[40] Investigators reported a significant inverse association between a 10% increase in the %TIR and CAN severity. Each 10% increase in %TAR (>180 mg/dL) was independently correlated with the presence of CAN. Other studies showed similar relationships between %TIR and other diabetes complications, including carotid intimal-media thickening,[41] diabetic neuropathy,[42, 43] retinopathy,[44, 45] nephropathy,[42, 46, 47] and CAN,[40, 48] a risk factor for increased mortality.[49]

The Present

In the real-world studies described previously, investigators observed significant improvements in glycemic control[22-32, 50] and quality of life measures.[22, 24, 26, 37, 38] Moreover, findings from large database analyses, such as those by Wright et al.[28] and Miller et al.[29] provide clear evidence of CGM efficacy within large and diverse diabetes populations. In our opinion, the RWE data supporting the benefits of CGM use in all individuals with diabetes, regardless of therapy, is incontestable. However, studies have also uncovered significant limitations in our healthcare systems, which serve as barriers to the full effectiveness of this technology.

For example, in a recent 12-month retrospective analysis of 1,329,061 Medicare beneficiaries who were treated with intensive insulin regimens, 38.14% were non-adherent to their prescribed glucose monitoring and 35.42% had no record of obtaining glucose monitoring supplies (35.42%).[14] Among the 629,514 beneficiaries with ≥2 comorbidities, 466,646 (74.13%) were either non-adherent to BGM or had no monitoring record. These types of findings have given rise to a number of key learnings explored more deeply in the following sections.

Racial/Ethnic and Socioeconomic Disparities

The body of evidence reporting disparities in healthcare quality and clinical outcomes among racial/ethnic minorities and individuals of low socioeconomic status continues to grow. It has been reported that young type 1 diabetes (T1D) patients who are covered by Medicaid are often treated with less intensive insulin regimens and receive fewer therapy changes.[51] This disparity was found to be particularly conspicuous among Hispanic and Black patients. We also know that T1D children/adolescents who are of lower socioeconomic status and covered by public health plans have higher HbA1c values, greater incidence of diabetic ketoacidosis (DKA), and diminished quality of life.[52-55]

While the prevalence of diabetes and its complications are disproportionately higher within racial/ethnic and low socioeconomic populations, the use of CGM and other diabetes technologies is disproportionately low,[56-58] with significant differences in use of or access to diabetes technology.[59-62] In a recent retrospective study of 227 T1D adults, Wirunsawanya et al. reported notable racial disparities in patterns of CGM use.[63] Among the 68 patients who used CGM, 47% were White, compared with 22% Hispanic and only 14% Black users. Investigators further observed that patients with government healthcare coverage were less likely to use CGM compared with patients with commercial healthcare coverage.

Similar disparities were reported in a cross-sectional, multicenter study of 300 young T1D adults (20 years), which included 99 (33%) White patients, 102 (34%) Hispanic patients, 64 (32%) Black patients.[61] Significantly more White patients (71%) had ever used CGM compared with Hispanic (37%) and Black (28%) patients, $p<0.001$. Importantly, Black and Hispanic participants had lower annual household incomes, less education, and higher neighborhood poverty, than White patients. Lai et al. reported similar findings of racial disparities in CGM initiation and continued use in a retrospective review of 1,509 T1D pediatric patients.[60] In their review of patient charts, investigators found that 726 patients had started CGM over the 3-year observation period. Among the CGM users, 392 (54%) were White, 239 (33%) were Hispanic, and 225 (31%) were Black, $p<0.001$. After one year of use, fewer Black (61%) patients than White (86%) and Hispanic (85%) patients were still using CGM. Reasons for discontinuation were not reported.

Although implicit bias likely plays a role in racial/ethnic disparities,[64-67] the influence of socioeconomic status must also be considered. It is known that a significantly higher percentage of Black and Hispanic people are more likely to live in low socioeconomic communities compared with White people.[68, 69] However, these disparities are not restricted to the U.S. In two recent reports from the U.K.,[56, 58] use of CGM among T1D adults and children/adolescents was lowest in the most economically deprived neighborhoods. Such findings provide important real world insights into the limited effectiveness of this technology in clinical settings where it may be most urgently needed.

Suboptimal Utilization of Diabetes Self-Management Education

Diabetes self-management education and support (DSMES) and medical nutrition therapy (MNT) have been shown to be cost-effective in reducing the acute and chronic complications of diabetes and diabetes-related hospitalizations.[70, 71] However, utilization of these services remains suboptimal.[72] In a 2014 analysis, investigators reported that only 6.8% of individuals with newly-diagnosed diabetes who are covered by commercial health insurance received DSMES within the first 12 months of diagnosis.[73] Among the Medicare diabetes population, which comprises approximately one third all diabetes in the U.S., only 5% used DSMES,[74] even though Medicare covers up to 10 hours of education during the first year of enrollment and up to 2 hours of follow-up education each calendar year thereafter.

Clinician Reluctance to Utilize Technology

Although endocrinologists have embraced CGM in their practices, not all patients have the resources or ability to access subspecialty care, particularly in rural areas.[75] As reported by Stewart in an early study, 75% of the counties in the U.S. have no endocrinologists, whereas 96% have primary care physicians.[75] As such, approximately 90% of individuals with diabetes receive their care in primary care settings.[76] Unfortunately, many primary care clinicians are reluctant to use CGM due to their unfamiliarity with the various devices, lack of confidence in interpreting and utilizing the glucose data for therapy decision making, uncertainty about which devices are best suited to specific patients, and the time required to access glucose data.[77-79] As reported by Grunberger et al. in a recent survey of 100 endocrinologists and 102 primary care clinicians in the U.S., 87.0% of endocrinologists reported using CGM compared with only 28.4% of primary care clinicians.[80] These real world observations provide important directions for new programmatic initiatives that might broaden and enhance the use of this technology in diabetes care.

The Future

Ongoing innovations in glucose monitoring technologies have prompted an increasing number of companies to begin developing new approaches to CGM. A recent article by Idlebrook reported that 39 new CGM systems are currently under development.[81] Many of these devices are non-invasive, whereas others are focusing on approaches never before explored for glucose monitoring, such as use of retinal imaging and infrared light to measure glucose molecules under the skin.[81]

While the future of CGM technologies is promising, the challenge of how to ensure that current and future technologies are accessible to everyone who would benefit from them remains daunting and is not addressed or informed by RCTs. In light of lessons learned so far, we believe the solution will require a rethinking and restructuring of how we deliver diabetes care to patients in the setting of their unique real world circumstances.

Provide Education/Training. Although adoption of CGM in primary care settings has been slow, a recent survey of 656 primary care clinicians found that the majority of respondents (72.3%) indicated that they would be likely to prescribe CGM with if they could receive appropriate education via individual training or workshops.[79] Although clinicians must invest time to learn about the various systems currently marketed, helping them develop expertise in interpreting and utilizing CGM data to optimize insulin titration and non-insulin therapies must be a key component of this training.[82-85]

Modify Electronic Medical Record (EMR) systems. The inability to upload glucose data directly into the electronic medical record (EMR) system of each practice is a major contributor to clinicians' reluctance to utilize CGM in their practices. Because most clinicians have no influence in addressing this issue directly, it is up to the various healthcare systems to compel software developers to modify their current EMR systems. The goal is to facilitate seamless upload and retrieval of CGM data that clinicians and other members of the healthcare team can easily access during patient visits. This, alone, would encourage more widespread use of CGM in primary care.

Promote a Team-Based Approach. There is substantial evidence that a team-based approach to diabetes patient management improves glycemic control, blood pressure and lipid levels in individuals with T2D, and this approach increases the proportion of patients who achieve established goals for these three metrics.[86] Creating a diabetes care team will require practices to establish protocols for patient referral and inter-team communication, define each team member's role, and allocate the office space necessary to function smoothly. Practices that do not have the personnel who are qualified in diabetes management should establish relationships with external professionals (Certified Diabetes Care and Education Specialists [CDCES], medical nutritionists, others) who can provide education and support to patients.

Streamline Preauthorization Requirements. Onerous documentation requirements to obtain preauthorizations for CGM and other technologies place additional time constraints on clinicians and staff in heavily-burdened, busy practices. Moreover, these requirements can have adverse effects on patient health. In a 2017 survey of 1,000 clinicians, 54% of respondents reported that the required preauthorization documentation for medications and medical devices always or often resulted in care delays and 92% reported that these delays had a significant or somewhat negative impact on clinical outcomes.[87] Fortunately, this issue is slowly being addressed as many public and private health insurers are now covering CGM as a pharmacy benefit, which greatly simplifies the preauthorization process.

Eliminate Barriers to Accessing DSMES and MNT Education. As discussed previously, only a small proportion of individuals with diabetes have received education and training in diabetes self-management. The reasons for such low participation are multifactorial, including transportation difficulties, patient apathy, low perceived seriousness of diabetes complications, lack of accessible services, and how services are structured and delivered.[72, 88-90] Apart from the logistical issues in terms of securing transportation to a certified DSMES provider, Medicare beneficiaries are hindered by other obstacles, including the need to obtain a referral from their primary healthcare provider, costly co-pays, and the inability to receive DSMES and MNT services on the same day.[91] Addressing these barriers requires close collaboration between all stakeholders -- clinicians, medical associations, insurers, and policy makers – working jointly to review and eliminate current requirements that restrict access and become creative in initiating and funding programs that enable all individuals to receive the education and training needed to effectively self-manage diabetes.

Expand CGM Coverage. Most public and private insurers now provide CGM coverage for individuals treated with intensive insulin regimens. However, expanding coverage to include individuals treated with less intensive insulin or non-insulin therapies has been slow despite a growing body of evidence supporting the CGM use in these populations.[28-32] This is an area of needed change, inasmuch as policy-making needs to keep pace with clinical evidence. The currently proposed Local Coverage Determination (LCD) from Medicare which could provide CGM coverage for patients on less-intense insulin regimens (e.g., basal insulin only) is a very encouraging development.[92] Given the increasing global prevalence of diabetes, and the strength of the evidence for effectiveness of CGM from RCTs and RWE, it is imperative that CGM is made available to all individuals who could benefit from its use.

Summary

Change in HbA1c continues to be a primary endpoint in most diabetes RCTs. However, this metric has several limitations as a measure of an individual's intra- and inter-day glycemic status. Although traditional blood glucose monitoring partially fills this gap, even the most frequent testing may miss critical glucose excursions. Use of CGM overcomes these limitations by automatically transmitting a constant stream of glucose data that provide information about the user's immediate and anticipated glycemic status. Utilizing download software, users and their clinicians can retrospectively assess the data and determine whether key glycemic goals (e.g., time in range, glycemic variability) are being met.

RCTs remain the gold standard for assessing the long-term efficacy of a given intervention when applied in highly structured, controlled environments. However, they do not fully inform about the effectiveness of the invention when used by individuals under real-world conditions. RWE provides this clinical information and gives insights regarding other barriers (e.g., economic, social, behavioral) to access and optimally utilize under circumstances of daily living.

Over the past several years, real-world prospective and retrospective studies have clearly demonstrated the clinical value of CGM in individuals treated with intensive insulin therapy.[22-27] More recently, RWE has shown that individuals treated with less-intensive therapies experience similar benefits,[22, 24, 26, 28-32, 37, 38] and they have provided needed evidence to support the use of established CGM metrics.[40-49] Moreover, findings from these studies have shed additional light on health disparities and even failures within the U.S. healthcare system that are limiting access to CGM and overall quality care.

Although some of these issues can be addressed at the clinic level by promoting the importance of self-management education to patients and transitioning to a team-based approach for patient care, others will require all stakeholders -- insurers, health systems, regulatory agencies and industry -- to examine issues and policies within their purviews and take the necessary steps to eliminate access barriers. Much improvement in clinical outcomes across the broad spectrum of diabetes awaits the results of such efforts.

Author Contribution Statement:

JRG III, CJB, and CGP wrote, reviewed and approved the manuscript for submission. JRG III, CJB, and CGP are the guarantors of this work and take responsibility for the integrity of the data and the accuracy of the content.

Disclosures:

JRG III has served on advisory boards and/or speaker bureaus for Abbott Diabetes Care, Novo Nordisk, Medtronic, and Boehringer Ingelheim.. CJB has served on advisory boards for Abbott Diabetes Care, Boehringer Ingelheim, Lexicon, Novo and Sanofi. CGP has received consulting fees from Abbott Diabetes Care, CeQur SA, Dexcom, Embecta, Lifescan, Mannkind, Provention Bio, Roche Diabetes Care, and Tandem.

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(FIGURE LEGENDS)

Figure 1. AGP Report