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ORIGINAL ARTICLE

Real-World Studies Support Use of Continuous Glucose Monitoring in Type 1 and Type 2 Diabetes Independently of Treatment Regimen

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Abstract

Numerous randomized controlled trials (RCTs) have demonstrated the glycemic benefits of continuous glucose monitoring (CGM) in management of type 1 diabetes (T1D) and type 2 diabetes. Although RCTs remain the gold standard clinical study design, findings from these trials do not necessarily reflect the effectiveness of CGM or reveal the feasibility and wider applications for use in broader real-life settings. This review evaluates recent real-world evidence (RWE) demonstrating the value of CGM to improve clinical outcomes, such as avoidance of severe hypoglycemic and hyperglycemic crises, and improved measures of psychological health and quality of life. Additionally, this review considers recent RWE for the role of CGM to enhance health care resource utilization, including prediction of T1D and applications in gestational diabetes, chronic kidney disease, and monitoring during surgery.

Keywords: CGM, Type 1 diabetes, Type 2 diabetes, RCTs, Observational, Hospitalizations.

Introduction

Well-designed, randomized controlled trials (RCTs) have traditionally been considered the highest level of trial evidence. Although they provide critical information about the efficacy of a given intervention (medication or medical device) when applied within tightly controlled clinical conditions, the results may not replicate how or if individuals will actually integrate the intervention into their daily lives, potentially resulting in an overestimation of efficacy. Moreover, RCTs may not reflect the effects of an intervention within the populations that have been excluded from the trial.

Another limitation of RCTs concerns the assessment of rapidly evolving diabetes technologies in meta-analyses and systematic reviews (MASRs). By the time enough studies have been completed for a robust MASR, subsequent improvements in accuracy, reliability, and convenience will render the results from MASRs outdated and potentially misleading in terms of the efficacy and safety of current technologies. This is particularly relevant to continuous glucose monitoring (CGM).

Given these limitations, there is growing recognition for the role of real-world evidence (RWE) generated by prospective, retrospective, and observational studies that fill the knowledge gap between the responses of individuals to an intervention within a controlled setting compared with patterns of response and clinical impact in real life. Recognizing the importance of real-world study designs, many payers and regulatory agencies now request pharmaceutical and medical device manufacturers to submit RWE in conjunction with findings from their RCTs when assessing the safety, effectiveness, and cost–benefit parameters of new medications and medical devices.[1–4]

Over the past decade, findings from several large RCTs have demonstrated the clinical value and utility of improving the overall glycemic status[5–10] and reducing hypoglycemia risk[5,7,11–13] in individuals with type 1 diabetes (T1D) and type 2 diabetes (T2D) who are treated with intensive insulin regimens. In this article, we review findings from recent real-world studies of CGM systems that provide greater insights into the clinical effectiveness and economic impact of this technology within various diabetic populations. We also discuss how CGM is being used to expand our understanding of diabetes in toto.

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Evidence of Clinical Effectiveness

As adoption of CGM continues to expand, we are seeing a growing number of large national and commercial database studies investigating the effects of CGM on A1C, hypoglycemia risk, and acute diabetes-related events in individuals with T1D[14–24] and T2D.[25–27]

Table 1 presents a summary of findings from the most recent real-world studies within the past 2 years.

T1D studies

A recent, prospective observational study assessed the impact of using flash CGM (FreeStyle Libre, Abbott Diabetes Care, Alameda, CA) in a cohort of 1913 T1D adults.[15] During the 12-month study period, there was a significant reduction in admissions for severe hypoglycemia and/or ketoacidosis (from 3.3% to 2.2%, $P = 0.031$), with fewer individuals reporting severe hypoglycemic events (from 14.6% to 7.8%, $P < 0.0001$). Reductions in the percentages of individuals who experienced hypoglycemic coma (from 2.7% to 1.1%, $P = 0.001$) and reported work absenteeism (from 5.8% to 2.9%, $P < 0.0001$) were also observed. Results from an earlier study showed similar findings among patients using other CGM devices, namely MiniMed Enlite (Medtronic, Inc., Northridge, CA); G4 PLATINUM (Dexcom, Inc., San Diego, CA); and FreeStyle Navigator II (Abbott Diabetes Care).[14] The use of these devices also showed favorable results in improving A1C, reducing hypoglycemia events and hospitalizations, and decreasing days absent from work.

Similar findings emerged from an analysis of a large Dutch registry that included 1365 individuals with diabetes, the majority of whom had T1D (77%).[16] Investigators reported that use of flash CGM was associated with significant A1C reductions after 12 months (from 8.0% to 7.4%, $P < 0.001$). Significant reductions in the percentage of patients experiencing any hypoglycemic event (from 93.1% to 91.0%, $P < 0.05$) and a decrease in the number of diabetes-related hospitalizations (from 144 to 22, $P < 0.001$) were also observed along with reductions in work absenteeism (from 18.6% to 7.8%, $P < 0.001$).

In a single-center cohort of 41 participants with T1D (aged 5–49 years), investigators assessed the long-term effects of initiating CGM (FreeStyle Libre, Dexcom G4, and MiniMed Guardian Sensor 3) in conjunction with insulin pump therapy on A1C and the incidence of hypoglycemia and microvascular disease. At follow-up (8.9 ± 2.8 years), A1C had decreased from 8.8% to 7.6% ($P = 0.051$), with significant reductions in severe hypoglycemia (from 9.7 to 2.2 per 100 patient-years, $P = 0.03$), but with a comparable incidence of newly diagnosed, diabetic microvascular complications.[32]

Similar A1C reductions were observed in a prospective observational study that assessed A1C changes in 900 adult T1D patients using flash CGM compared with 518 patients who continued usual care with traditional blood glucose monitoring (BGM).[18] Users of flash CGM with a baseline A1C >7.5% showed a significant reduction of A1C over an 8-month study period (median –0.6%, $P < 0.001$), whereas no changes in A1C were observed with BGM use. Among flash CGM users, there was a 48.8% increase in those achieving an A1C <7.5% and the number of those with an A1C >9.0% was more than halved. Although flash CGM users reported more symptomatic and asymptomatic hypoglycemia, this is likely to derive from heightened awareness due to having access to continuous glucose data through frequent scanning. Importantly, there were no significant changes in severe hypoglycemia.

An earlier study of 120 T1D adults who were followed for 12 months after initiating flash CGM found significant decreases in A1C levels from baseline at 3 months (from 8.5% to 7.8%, $P < 0.001$), but with a slight increase to 7.9% at 12 months.[22] These improvements were accompanied by reduction in fear of hypoglycemia, which is often a major obstacle to achieving optimal glycemic control.[33,34] As noted in some other studies,[21] there was a slight, but statistically significant, ($P < 0.05$) increase in the number (but not duration) of hypoglycemic events at 12 months, which correlated with improvements in A1C and may be attributed largely to awareness with use of CGM. However, in a prospective observational study that compared flash CGM with BGM use in a cohort of 334 T1D children/adolescents, there was a 53% ($P = 0.012$) reduction in cases of severe hypoglycemia among users of flash CGM compared with those using BGM, although A1C was not significantly altered in either group.[35] The majority (83.2%) of patients who switched from BGM to using flash CGM were still using their device after median use of 5.3 months.

T2D studies

About 20%–30% of patients with T2D eventually require insulin therapy, enabling substantial reductions in A1C levels, acute diabetes-related adverse events (ADEs), and all-cause hospitalizations (ACHs).[21,27] Although a majority of insulin-treated T2D patients receive only basal insulin with or without other glucose-lowering agents (rather than basal–bolus injections or pump therapy), CGM still offers an opportunity to optimize glycemic control.

A retrospective chart review of 363 T2D adults from three European countries assessed the effectiveness of flash CGM use in conjunction with basal–bolus therapy.[21] After >90 days following initiation of flash CGM, A1C levels were significantly lower: –0.9% (Austria), –0.8% (France), and –0.9% (Germany), all $P < 0.0001$. The impact of this magnitude of A1C reductions after acquiring a flash CGM device is reflected in findings from an analysis of IBM MarketScan Commercial Claims and Medicare Supplemental databases.[27] This retrospective real-world analysis of a cohort of 2463 T2D adults treated with short- or rapid-acting insulin noted significant reductions in ADEs (from 0.180 to 0.072 events/patient-year, $P < 0.001$) and ACHs (from 0.420 to 0.283 events/patient-year, $P < 0.001$) during the 6 months after acquiring their flash CGM device compared with the 6-month period before acquisition. These improvements occurred regardless of age or gender.

Recent studies of flash CGM in T2D adults treated with nonintensive therapies have shown similar findings.[30,31] In a Canadian chart review of 91 T2D adults managed with basal insulin therapy, there were significant A1C reductions (–0.8%, $P < 0.0001$) after 3–6 months of flash CGM use.[30] A subgroup analysis comparing patients with baseline A1C of <9.0% and >9.0% showed clinically significant A1C reductions in both groups, but with most notable reductions occurring in the higher A1C group (–1.6%, $P < 0.0001$). A U.S. chart review study of 100 T2D adults treated with basal

Table 1. Real-World Studies of Continuous Glucose Monitoring Use in Populations with Type 1 Diabetes and Type 2 Diabetes

Studies	*Design*	*Study population*	*Outcome measures following CGM initiation*	*Findings*
T1D				
Charleer[15]	A 12-month, prospective, observational multicenter cohort (Belgium)	$N=1913$ T1D Age: 45.8 ± 15.3 years	Hospitalizations with DKA and/or SH Absenteeism Treatment satisfaction	Hospitalizations decreased from 3.3% to 2.2% ($P=0.031$) Severe hypoglycemic events decreased from 14.6% to 7.8% ($P<0.0001$) Hypoglycemic comas decreased from 2.7% to 1.1% ($P=0.001$) Fewer people were absent from work (2.9% vs. 5.8%, $P<0.0001$) Questionnaire-derived measures of treatment satisfaction improved
Sandig[17]	Cross-sectional analysis (German/Austrian/Swiss Prospective Diabetes Follow-up [DPV] Registry)	$N=233$ T1D Age: ≥18 years	CGM metrics Time in range %TIR (70–180 mg/dL) Time below range %TBR (<70 mg/dL) Time above range %TAR (>180 mg/dL) Glycemic variability (% CV)	Participants aged ≥30 vs. <30 years spent more TIR (54% vs. 49%), more TBR (7% vs. 5%), less TAR (38% vs. 46%), and with a lower % CV (36% vs. 37%) Highest TIR and lowest time with sensor glucose >250 mg/dL observed in those treated with CSII and CGM
Šoupal[24]	A 3-year, nonrandomized, prospective 4-arm study	$N=$T1D 22 (CGM+MDI) $N=$T1D 26 (CGM+CSII) $N=$T1D 21 (BGM+MDI) $N=$T1D 25 (BGM+CSII) Age: ≥18 years	A1C change CGM metrics Time in range %TIR (70–180 mg/dL) Time below range %TBR (<70 mg/dL)	Greater A1C reductions from baseline at 3 years in the CGM+MDI and CGM+CSII groups (–1.2%, $P=0.0002$, and –1.3%, $P<0.0001$, respectively) compared with the BGM+MDI (–0.3%, $P=0.3574$) and BGM+CSII (–0.6%, $P=0.1000$) groups No significant difference in A1C reduction between the CGM+MDI and CGM+CSII groups ($P=0.61$) Significant increases in %TIR and reductions in %TBR in the CGM subgroups, but not in the BGM subgroups
T1D and T2D				
Roussel[28]	A 12-month, longitudinal retrospective cohort, pre- and postinitiation of flash CGM in France (French National Claims Database)	$N=33,165$ T1D Age: 8 to >75 years $N=40,846$ T2D Age: 16 to >75 years	Hospitalization for acute diabetes event Hospitalization for DKA	Significant reductions in hospitalizations for acute diabetes complications in T1D and T2D patients (–49.0% and –39.4%, respectively) Hospitalization rates for DKA fell by 55.0% (from 2508 patients to 1128 patients) Percentage of patients with at least one hospitalization for diabetes-related coma lower by 35.7% (T1D, –39.6%; T2D, –31.9%)

(*continued*)

TABLE 1. (CONTINUED)

Studies	*Design*	*Study population*	*Outcome measures following CGM initiation*	*Findings*
Eeg-Olofsson[23]	A 12-month, retrospective observational study, pre- and postacquisition of flash CGM (Swedish National Diabetes Register)	*N* = 39,554 T1D or T2D Age: ≥18 years	A1C change	Significant A1C reductions achieved and sustained at 12 months in T1D (–0.44%) and T2D (–0.66%)
Hirsch[29]	A 12-month, retrospective observational study, pre- and post-CGM acquisition (IBM MarketScan Commercial Claims and Medicare Supplemental databases)	*N* = 12,521 T1D or T2D Age: ≥18 years Short- or rapid-acting insulin	ADEs for hypoglycemia or hyperglycemia	Reductions in from 0.245 to 0.132 events/patient-year (HR: 0.54 [95% CI: 0.49–0.59]; $P < 0.001$) No association between ADE reductions and history of BGM daily frequency (≥4 vs. <4)
T2D				
Bergenstal[27]	A 12-month, retrospective observational study, pre- and post-CGM acquisition (IBM MarketScan Commercial Claims and Medicare Supplemental databases)	*N* = 2463 T2D Age: ≥18 years Short- or rapid-acting insulin	ADEs and ACHs	ADE rates decreased from 0.180 to 0.072 events/patient-year HR: 0.39 [0.30, 0.51]; $P < 0.001$) ACH rates decreased from 0.420 to 0.283 events/patient-year (HR: 0.68 [0.59 0.78]; $P < 0.001$)
Miller[25]	A 12-month, retrospective observational study, pre- and post-CGM acquisition (IBM MarketScan Commercial Claims and Medicare Supplemental databases)	*N* = 10,282 T2D Age: ≥18 years Basal insulin or noninsulin therapy	ADEs and ACHs	ADE rates decreased from 0.076 to 0.052 events/patient-year (HR: 0.68 [0.58 0.80]; $P < 0.001$) ACH rates decreased from 0.177 to 0.151 events/patient-year (HR: 0.85 [0.77 0.94]; $P = 0.002$)
Wright[26]	A 12-month, retrospective observational study, pre- and post-CGM acquisition (IBM Explorys database)	*N* = 1034 T2D Age: ≥18 years Basal insulin or noninsulin therapy	A1C change	Reductions in A1C within the full cohort (from 10.1% ± 1.7% to 8.6% ± 1.8%, $P < 0.001$) Greatest reductions in patients with baseline A1C ≥12.0% (–3.7%, $P < 0.001$) Reductions in A1C in both treatment groups (basal insulin, –1.1%; and noninsulin –1.6%, both $P < 0.001$)
Elliot[30]	A 3- to 6-month, retrospective chart review	*N* = 91 T2D Age: ≥18 years Basal insulin	A1C change	Reductions in A1C after ≥3 months of CGM use (–0.8% ± 1.1%, $P < 0.0001$) Subgroup analysis by baseline A1C (<9.0% vs. ≥9.0%) showed A1C reductions in both groups (–0.5% ± 0.8% and 1.6% ± 1.3%, $P < 0.0001$, respectively)

(*continued*)

TABLE 1. (CONTINUED)

Studies	Design	Study population	Outcome measures following CGM initiation	Findings
Carlson[31]	A 12-month, retrospective chart review, pre- and post-CGM acquisition	$N = 100$ T2D Age: ≥18 years Basal insulin	A1C change	Reduction in A1C after ≥3 months of CGM use (−1.4% ± 1.3%, $P < 0.0001$) Subgroup analysis by baseline A1C (<9.0% vs. ≥9.0%) showed significant A1C reductions in both groups (−0.8% ± 0.7% and 1.7% ± 1.4%, both $P < 0.0001$, respectively)
Kröger[21]	A 3- to 6-month, pragmatic, parallel, European, retrospective, noninterventional chart review (Austria, French, and German Registries)	$N = 363$ T2D adults	A1C change Subgroup analyses by age (<65 vs. ≥65 years), duration of insulin therapy (<9 vs. ≥9 years), BMI (<30 vs. ≥30 kg/m^2), and gender	Reduction in A1C in all three countries: −0.9% (Austria), −0.8% (France), and −0.9% (Germany), all $P < 0.0001$ A1C improvements across all subgroups, with no significant differences between subgroups

ACH, all-cause hospitalization; ADEs, acute diabetes-related adverse events; BGM, blood glucose monitoring; BMI, body–mass index; CGM, continuous glucose monitoring; CV, coefficient of variation; CSII, continuous subcutaneous insulin infusion; DKA, diabetic ketoacidosis; DPV, Diabetes Prospective Follow-up Registry; HR, hazard ratio; IBM; MDI, multiple daily insulin injections; QoL, quality of life; SH, severe hypoglycemia; SH; Studies; T1D, type 1 diabetes; T2D, type 2 diabetes; TAR, time above range; TBR, time below range; TIR, time in range.

insulin therapy showed similar reductions in A1C after 3–6 months of flash CGM, with the largest reductions (−1.7%, $P < 0.0001$) seen in those with baseline >9.0 A1C.[31]

Findings of decreased rates of ADEs and ACHs have also been reported in a cohort of 10,282 adult T2D patients treated with nonintensive or noninsulin therapy.[25] Retrospective analysis of the MarketScan databases revealed significant decreases in ADEs and ACHs at 6 months postacquisition of a flash CGM device (from 0.076 to 0.052 events/patient-year, $P < 0.001$, and from 0.177 to 0.151 events/patient-year, $P = 0.002$, respectively). Using a similar study design, an analysis of the Explorys commercial databases assessed the impact of flash CGM acquisition in 1034 poorly controlled T2D adults (baseline A1C 10.1%) treated with basal insulin ($n = 306$) or noninsulin therapy ($n = 728$).[26] At 6 months postacquisition of a flash CGM device, significant reductions in A1C were observed in the basal insulin group (−1.1%) and noninsulin treatment group (−1.6%), both $P < 0.001$.

Intermittent use of CGM has also been demonstrated to improve glycemic control in T2D patients treated with less-intensive therapies. Findings from two studies, which assessed changes in A1C in T2D adults enrolled in the Onduo Virtual Diabetes Clinic telehealth program, showed that intermittent use of CGM was strongly associated with significant reductions in A1C.[36,37] In 55 patients with mean baseline A1C of 8.9%, intermittent use of the Dexcom G5 device resulted in a 1.6% reduction in A1C from baseline ($P < 0.001$).[36] In a larger study ($n = 372$) of an Onduo population with 7.7% A1C at baseline, Bergenstal et al. observed a smaller, but significant, reduction (–0.6%, $P < 0.001$) from baseline.[37] However, the reduction among those with >9.0% baseline A1C was notably greater (–2.6%, $P < 0.001$).

Inpatient outcomes

Achieving and maintaining glycemic control in critically ill patients have been shown to profoundly impact clinical outcomes,[38] especially in patients with diabetes and patients being treated with insulin infusions for hyperglycemic crises such as diabetic ketoacidosis or hyperosmolar hyperglycemic state.[39] Managing glycemic status also plays an important role in reducing viral load and infection duration in patients with diabetes.[40]

As demonstrated in a single-center cohort study of 44 patients with diagnosed T2D and 16 with new-onset hyperglycemia,[41] glycemic metrics were improved, and composite complications were reduced when using flash CGM during insulin treatment. Across the 190,080 available CGM data points, 72.5% of values were within the target glucose range of 70–180 mg/dL, 22% were >180 mg/dL, and 3% were <70 mg/dL. During treatment, the coefficient of variation (% CV) was 30%. Although no associations between time in range (TIR) and the composite complications were observed, patients who spent more time with glucose >180 mg/dL had higher complication rates than those who maintained target glucose levels (22.5% vs. 16%, $P = 0.04$).

In another single-center cohort study, CGM data (Dexcom G6) from 30 diabetic patients during the first 24 h of admission to intensive care with severe coronavirus disease 2019 (COVID-19) infection were compared with glucose values from arterial line point-of-care (POC) values.[42] CGM data were used to adjust insulin if CGM values were within 20%

of POC values, and although some discordance between CGM and POC values was observed in 11 patients, the differences were not considered clinically significant. During the observation period, mean sensor glucose decreased from 235.7 ± 42.1 mg/dL to 202.7 ± 37.6 mg/dL with the use of CGM. Additionally, most (63%) of the attending nurses reported that CGM was helpful for improving patient care and 49% indicated that use of CGM reduced their personal protective equipment utilization.

Improvements in psychosocial measures

In many of the current studies that showed significant associations between CGM use and improvements in glycemic measures, investigators have also reported increased treatment satisfaction,[15,20] less hypoglycemia fear,[20,22] enhanced sense of well-being,[20] and improvements in other health-related measures[15,16,18–20] associated with CGM use. For example, further analysis of a cohort of mostly T1D individuals described earlier[16] found improvements in quality of life (QoL) measures and better patient engagement with their self-management regimens.[43] Flash CGM users reported reduced diabetes burden, as assessed with the SF-12^{v2} and EQ-5D-3L questionnaires. Participants also reported more frequent insulin dose adjustments (80%) and less worry about their diabetes among family members (62%). The majority (81.7%) stated that they felt no inhibitions about measuring their glucose in the presence of strangers.

Studies that focused primarily on QoL outcomes in T1D children, adolescents, and young adults using CGM have shown similar improvements in psychosocial measures, including significant improvements in overall QoL ($P = 0.014$), lessening of diabetes symptoms ($P = 0.018$), and reductions in barriers to treatment ($P = 0.035$).[19] In a 2019 study of 33 T1D adolescents and young adults, investigators reported significant increases in treatment satisfaction and overall well-being, both $P < 0.001$, after 12 weeks of flash CGM use.[20]

An Australian study that recruited 38 T1D adolescents (aged >12 years) and their parents ($n = 60$) assessed changes in psychosocial measures after 2 months of CGM use.[44] Among parents, significant reductions in the total hypoglycemia fear score and worry subscore were observed (both $P = 0.004$), with improvements in reported sleep quality. Treatment satisfaction increased in both the patient and parent groups, and significant reductions in the Gold hypoglycemia awareness score were reported (from 26.3% to 10.5%, $P = 0.031$).

Use of advanced CGM features

Innovations in CGM technologies have resulted in a number of advanced features that have been shown to improve glycemic control and reduce hypoglycemia risk in individuals with T1D and T2D. For example, in a retrospective analysis of 15,000 T1D children and adolescents, 94.8% of whom used the Dexcom sharing feature,[45] use of this feature was associated with lower mean glucose values, a higher percentage of time spent in the target glucose range (70–180 mg/dL), and fewer episodes of hypoglycemia and hyperglycemia.

A recent study of the Guardian Connect System with the MiniMed Enlite sensor retrospectively analyzed CGM data from individuals with T1D ($n = 2692$), T2D ($n = 93$), or gestational diabetes ($n = 5$). When patients utilized the predictive alerts function, 59% of low glucose excursions and 39% of high glucose excursions were prevented.[46]

Studies that Inform Clinicians and Guide Therapy

In addition to improving daily self-management, CGM has broadened our appreciation of risk factors and clinical assessments associated with diabetes.

Risk factors

Gender differences in hypoglycemia risk were examined in a post hoc analysis of a single-center prospective trial of 102 adult T2D inpatients (male, $n = 52$; female, $n = 50$) treated with intensive insulin therapy.[47] Patients underwent a standard bread meal test at baseline and were monitored with CGM during the last 4 of 7 days on insulin pump therapy. Although male patients required lower doses of insulin to maintain optimized glycemic control, they spent more time with glucose levels <70 mg/dL than their female counterparts (3.2% vs. 0.9%, $P < 0.01\%$, respectively), with a higher of incidence of hypoglycemia (20/52 vs. 9/50, $P = 0.022$).

A study of CGM in 77 women with gestational diabetes (GDM) investigated whether specific patterns of hyperglycemia at different times of the day could predict maternal–fetal complications.[48] After placing the women on prospective CGM for 6 days between 26 and 32 weeks of gestation, investigators observed a statistically significant relationship between the time spent in hyperglycemia after lunch and fetal complications, including macrosomia ($P = 0.035$) and large-for-gestational age infants ($P = 0.010$). There was also a 24% increase in the probability of initiating glucose-lowering therapies for every additional percentage point of time above range.

CGM has also been used to predict glycemic control based on socioeconomic status based on the Index of Relative Socio-economic Disadvantage (IRSD),[49] which measures disadvantage (e.g., poverty, deprivation, and social exclusion) at an area level (e.g., neighborhood and community), not at an individual level.[50] Among 300 adult T2D patients assessed in the General Practice Optimising Structured Monitoring To Improve Clinical outcomes (GP-OSMOTIC) randomized study, glucose data from the FreeStyle Libre Pro CGM system revealed that those who were least disadvantaged had higher TIR and lower A1C values than those who were most disadvantaged.[51] However, there was no association between the educational level and glycemic status.

CGM has been used to assess the appropriateness of a hospital protocol for managing patients postcardiovascular surgery.[52] Glycemic variability was recorded in 76 patients during elective cardiovascular surgery and postoperative management with continuous intravenous insulin infusion in the intensive care unit (ICU) and when injection therapy was introduced after oral food intake was initiated. While the study confirmed that the protocol was adequate during continuous subcutaneous insulin infusion treatment, it exposed changes needed to improve the injection therapy protocol.

Assessments

Although measurements of A1C and fructosamine are often used to monitor glycemic status in individuals without chronic kidney disease, these methods are limited in their

utility to predict the risk of acute glycemic events and to assess glycemic control in patients treated with dialysis. In a prospective study of 104 T2D patients with end-stage renal disease, blinded CGM was recorded for two 6-day periods separated by 2 weeks, in conjunction with A1C and fructosamine measurements.[53] When compared with CGM data, fructosamine was significantly biased by age, body–mass index, serum iron concentration, transferrin saturation, and albuminuria. In addition, A1C values were underestimated in patients with albuminuria.

The utility of CGM in predicting the onset of T1D was assessed in 23 antibody-positive (Ab+) participants in the Diabetes Autoimmunity Study in the Young (DAISY), which prospectively follows children who are at increased risk for developing islet autoantibodies and T1D.[54] Investigators found that spending ≥18% of time at >140 mg/dL was a strong predictor of progression to clinical diabetes in Ab+ children. These findings are particularly valuable in light of the development of new medications such as anti-CD3 monoclonal antibodies that have been shown to delay progression to T1D in high-risk individuals.[55,56]

Conclusions

Large RCTs have clearly demonstrated the benefits of CGM use in individuals with diabetes who are treated with intensive insulin therapy.[5–13] A growing number of real-world observational and prospective studies are confirming these findings and demonstrating similar benefits in T2D patients who are treated with less-intensive therapy.[25,26,30,31] Results from these studies suggest that wider use of CGM within the broader diabetic population could increase overall glycemic control and improve the effectiveness while reducing the enduring cost of diabetes health care. Moreover, as studies emerge to further elaborate on the utility of CGM to identify risk of complications, improve care of inpatients, and predict the development and progression of T1D, we anticipate applications of CGM in broader disease management and research.

Authors' Contributions

J.R.G. III and C.J.B. wrote, reviewed, and approved the manuscript for submission. C.J.B. and J.R.G. III are the guarantors of this work and take responsibility for the integrity of the data and accuracy of the content.

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References

1. Khosla S, White R, Medina J, et al.: Real world evidence (RWE)—a disruptive innovation or the quiet evolution of medical evidence generation? Version 2. F1000Res 2018;7:111.
2. Food and Drug Administration (FDA) Use of real-world evidence to support regulatory decision-making for medical devices. April 5, 2017. https://www.fda.gov/downloads/medicaldevices/deviceregulationand-guidance/guidancedocuments/ucm513027.pdf (accessed March 30, 2019).
3. Resnic FS, Matheny ME: Medical devices in the real world. N Engl J Med 2018;378:595–597.
4. Katkade VB, Sanders KN, Zou KH: Real world data: an opportunity to supplement existing evidence for the use of long-established medicines in health care decision making. J Multidiscip Healthc 2018;11:295–304.
5. Haak T, Hanaire H, Ajjan 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.
6. 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 randomized clinical trial. JAMA 2017;317:371–378.
7. 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.
8. Beck RW, Riddlesworth TD, Ruedy K, et al.: Continuous glucose monitoring versus usual care in patients with type 2 diabetes receiving multiple daily insulin injections: a randomized trial. Ann Intern Med 2017;167:365–374.
9. Lind M, Polonsky W, Hirsch IB: Continuous glucose monitoring vs conventional therapy for glycemic control in adults with type 1 diabetes treated with multiple daily insulin injections: the GOLD randomized clinical trial. JAMA 2017;317:379–387.
10. Aleppo G, Ruedy KJ, Riddlesworth TD, et al.: 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 2017;40:538–545.
11. Heinemann L, Guido Freckmann G, Gabriele Faber-Heinemann G, et al.: Benefits of continuous glucose monitoring use in adults with type 1 diabetes and impaired hypoglycaemia awareness and/or severe hypoglycaemia treated with multiple daily insulin injections: results of the multicentre, randomised controlled HypoDE study. Lancet 2018;391:1367–1377.
12. Ólafsdóttir AF, Polonsky W, Bolinder J, et al.: A randomized clinical trial of the effect of continuous glucose monitoring on nocturnal hypoglycemia, daytime hypoglycemia, glycemic variability, and hypoglycemia confidence in persons with type 1 diabetes treated with multiple daily insulin injections (GOLD-3). Diabetes Technol Ther 2018;20:274–284.
13. Oskarsson 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 2018;61:539–550.

14. Charleer S, Mathieu C, Nobels F, et al.: Effect of continuous glucose monitoring on glycemic control, acute admissions, and quality of life: a real-world study. Clin Endocrinol Metab 2018;103:1224–1232.
15. Charleer S, De Block C, Van Huffel L, et al.: Quality of life and glucose control after 1 year of nationwide reimbursement of intermittently scanned continuous glucose monitoring in adults living with type 1 diabetes (FUTURE): a prospective observational real-world cohort study. Diabetes Care 2020;43:389–397.
16. Fokkert M, van Dijk P, Edens M, et al.: Improved well-being and decreased disease burden after 1-year use of flash glucose monitoring (FLARE-NL4). BMJ Open Diabetes Res Care 2019;7:e000809.
17. Sandig D, Grimsmann J, Reinauer C, et al.: Continuous glucose monitoring in adults with type 1 diabetes: real-world data from the German/Austrian prospective diabetes follow-up registry. Diabetes Technol Ther 2020;22:602–612.
18. Tyndall V, Stimson RH, Zammitt NN, et al.: Marked improvement in A1C following commencement of flash glucose monitoring in people with type 1 diabetes. Diabetologia 2019;62:1349–1356.
19. Pintus D: Freestyle libre flash glucose monitoring improves patient quality of life measures in children with Type 1 diabetes mellitus (T1DM) with appropriate provision of education and support by healthcare professionals. Diabetes Metab Syndr 2019;13:2923–2926.
20. Al Hayek AA, Al Dawish MA: The potential impact of the FreeStyle libre flash glucose monitoring system on mental well-being and treatment satisfaction in patients with type 1 diabetes: a prospective study. Diabetes Ther 2019;10:1239–1248.
21. Kröger J, Fasching P, Hanaire H: Three European retrospective real-world chart review studies to determine the effectiveness of flash glucose monitoring on A1C in adults with type 2 diabetes. Diabetes Ther 2020;11:279–291.
22. Paris I, Henry C, Pirard F, et al.: The new FreeStyle Libre Flash Glucose Monitoring System improves the glycaemic control in a cohort of people with type 1 diabetes followed in real-life conditions over a period of one year. Endocrinol Diab Metab 2018;1:e00023.
23. Eeg-Olofsson K, Svensson A-M, Franzén S, et al.: Sustainable A1C decrease at 12 months for adults with Type 1 and Type 2 Diabetes using the FreeStyle Libre® system: a study within the National Diabetes Register in Sweden. Diabetes 2020;69(Supplement 1):74-LB-P.
24. Šoupal J, Petruželková L, Grunberger G, et al.: Glycemic outcomes in adults with T1D are impacted more by continuous glucose monitoring than by insulin delivery method: 3 years of follow-up from the COMISAIR study. Diabetes Care 2020;43:37–43.
25. Miller E, Kerr MSD, Roberts GJ, et al.: FreeStyle Libre® system use associated with reduction in acute diabetes events and all-cause hospitalizations in patients with type 2 diabetes without bolus insulin. Am J Manag Care 2021 (In Press).
26. Wright EE, Kerr MSD, Reyes IJ, et al.: Use of flash continuous glucose monitoring is associated with A1C reduction in people with type 2 diabetes treated with basal insulin or non-insulin therapy. Diabetes Spectr 2021;34:184–189.
27. Bergenstal RM, Kerr MSD, Roberts GJ, et al.: Flash CGM is associated with reduced diabetes events and hospitalizations in insulin-treated type 2 diabetes. J Endocr Soc 2021;5:bvab013.
28. Roussel R, Riveline J-P, Vicaut E, et al.: Important drop rate of acute diabetes complications in people with type 1 or type 2 diabetes after initiation of flash glucose monitoring in france: the RELIEF study. Diabetes Care 2021;44:1–9.
29. Hirsch IB, Kerr MSD, Roberts GJ, et al.: Utilization of continuous glucose monitors is associated with reduction in inpatient and outpatient emergency acute diabetes events regardless of prior blood test strip usage. Diabetes 2020; 69(Supplement 1):875-P.
30. Elliot T, Beharry R, Tsoukas M, et al.: Glucose control after initiation of flash glucose monitoring in type 2 diabetes managed with basal insulin; A retrospective real-world chart review study from Canada. Advanced Technologies & Treatments for Diabetes (ATTD), Virtual, June 2–5, 2021. A-795.
31. Carlson AL, Daniel TD, Desantis A, et al.: Glucose control after initiation of flash glucose monitoring in type 2 diabetes managed with basal insulin; a retrospective real-world chart review study from the US. American Diabetes Association (ADA) 81st Scientific Sessions, Virtual June 25–29, 2021. LB-6626.
32. Senn J-D, Fischli S, Slahor L, et al.: Long-term effects of initiating continuous subcutaneous insulin infusion (CSII) and continuous glucose monitoring (CGM) in people with type 1 diabetes and unsatisfactory diabetes control. J Clin Med 2019;8:394.
33. Willis WD, Diago-Cabezudo JI, Madec-Hily A, Aslam A: Medical resource use, disturbance of daily life and burden of hypoglycemia in insulin-treated patients with diabetes: results from a European online survey. Expert Rev Pharmacoecon Outcomes Res 2013;13:123–130.
34. Perlmuter LC, Flanagan BP, Shah PH, Singh SP: Glycemic control and hypoglycemia. Diabetes Care 2008;31:2072–2076.
35. Messaaoui A, Tenoutasse S, Crenier L: Flash glucose monitoring accepted in daily life of children and adolescents with type 1 diabetes and reduction of severe hypoglycemia in real-life use. Diabetes Technol Ther 2019;21:329–335.
36. Majithia AR, Kusiak CM, Lee AA, et al.: Glycemic outcomes in adults with type 2 diabetes participating in a continuous glucose monitor–driven virtual diabetes clinic: prospective trial. J Med Internet Res 2020;22:e21778.
37. Bergenstal RM, Layne JE, Zisser H, et al.: Remote application and use of real-time continuous glucose monitoring by adults with type 2 diabetes in a virtual diabetes clinic. Diabetes Technol Ther 2021;23:128–132.
38. Yao RQ, Ren C, Wu GS, et al.: Is intensive glucose control bad for critically ill patients? A systematic review and meta-analysis. Int J Biol Sci 2020;16:1658–1675.
39. Kim N-Y, Ha E, Moon JS, et al.: Acute hyperglycemic crises with coronavirus disease-19: case reports. Diabetes Metab J 2020;44:349–353.
40. Peric S, Stulnig TM. Diabetes and COVID-19: Disease-Management-People. Wien Klin Wochenschr 2020;132: 356–361.
41. Gómez AM, Henao DC, Muñoz OM, et al.: Glycemic control metrics using flash glucose monitoring and hospital complications in patients with COVID-19. Diabetes Metab Syndr 2021;15:499–503.
42. Chow KW, Kelly DJ, Rieff MC, et al.: Outcomes and healthcare provider perceptions of real-time continuous glucose monitoring (rtCGM) in patients with diabetes and COVID-19 admitted to the ICU. J Diabetes Sci Technol 2021;15:607–614.

43. Wang P, Luo N, Tai ES, Thumboo J: The EQ-5D-5L is more discriminative than the EQ-5D-3L in patients with diabetes in Singapore. Value Heal Reg Issues Elsevier 2016;9:57–62.
44. Burckhardt M-A, Abraham MD, Mountain J, et al.: Improvement in psychosocial outcomes in children with type 1 diabetes and their parents following subsidy for continuous glucose monitoring. Diabetes Technol Ther 2019;21:575–580.
45. Welsh JB, Derdzinski M, Parker AS, et al.: Real-time sharing and following of continuous glucose monitoring data in youth. Diabetes Ther 2019;10:751–755.
46. Abraham SB, Arunachalam S, Zhong A, et al.: Improved real-world glycemic control with continuous glucose monitoring system predictive alerts. J Diabetes Sci Technol 2021;15:91–97.
47. Li F-F, Zhang Y, Zhang W-L, et al.: Male patients with longstanding type 2 diabetes have a higher incidence of hypoglycemia compared with female patients. Diabetes Ther 2018;9:1969–1977.
48. Márquez-Pardo R, Torres-Barea I, Córdoba-Doña J-A, et al.: Continuous glucose monitoring and glycemic patterns in pregnant women with gestational diabetes mellitus. Diabetes Technol Ther 2020;22:271–277.
49. Walker R, Hiller JE: The index of relative socio-economic disadvantage: general population views on indicators used to determine area-based disadvantage. Aust N Z J Public Health 2005;29:442–447.
50. Australian Bureau of Statistics. Socio-Economic Indexes for Areas (SEIFA). 2011. https://www.ausstats.abs.gov.au/ausstats/subscriber.nsf/0/22CEDA8038AF7A0DCA257B3B00116E34/$File/2033.0.55.001%20seifa%202011%20technical%20paper.pdf (accesed May 6, 2021).
51. Tan ML, Manski-Nankervis J-O, Thuraisingam S, et al.: Socioeconomic status and time in glucose target range in people with type 2 diabetes: a baseline analysis of the GP-OSMOTIC study. BMC Endocr Disord 2018;18:47.
52. Sato H, Hosojima M, Ishikawa T, et al.: Glucose variability based on continuous glucose monitoring assessment is associated with postoperative complications after cardiovascular surgery. Ann Thorac Cardiovasc Surg 2017;23:239–247.
53. Zelnick LR, Batacchi ZO, Ahmad I, et al.: Continuous glucose monitoring and use of alternative markers to assess glycemia in chronic kidney disease. Diabetes Care 2020;43:2379–2387.
54. Steck AK, Dong F, Iman Taki I, et al.: Continuous glucose monitoring predicts progression to diabetes in autoantibody positive children. J Clin Endocrinol Metab 2019;104:3337–3344.
55. Herold KC, Bundy BN, Long SA, et al.: An anti-CD3 antibody, teplizumab, in relatives at risk for type 1 diabetes. N Engl J Med 2019;381:603–613.
56. Sims EK, Bundy BN, Stier K, et al.: Teplizumab improves and stabilizes beta cell function in antibody-positive high-risk individuals. Sci Transl Med 2021;13:eabc8980.

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