Clinical Pharmacology in Drug Development
2018, 7(7) 676–683
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DOI: 10.1002/cpdd.437

Tracking the Sugar Rush: Incorporating Continuous Glucose Monitoring Into Multisite Early Clinical Research With Type 2 Diabetes Subjects

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Abstract

Continuous glucose monitoring (CGM) systems allow patients with diabetes mellitus to closely track glucose concentrations over several days, identify trends in glucose levels, and avoid glucose excursions. This technology has not only advanced diabetes mellitus management but has increased patient safety through greater glycemic awareness. Due to these attributes, CGM is now being applied in therapeutic research as a pharmacodynamic tool to support early clinical drug development programs. However, to date only a handful of studies have utilized CGM in type 2 diabetes mellitus (T2DM) drug development. A potential barrier from fostering greater use of CGM in clinical development may be related to concerns over subject variability. Therefore, we investigated a key consideration when implementing CGM into early clinical research studies: daily variation within patients with T2DM from multiple clinical research units. From 24 patients with T2DM, we observed strong daily reproducibility (Pearson R = 0.86, $P < .0001$) in CGM results and found that this technique is practical for multisite studies. Altogether, with low daily variability, CGM is a powerful pharmacodynamic tool for drug efficacy and safety monitoring.

Keywords

diabetes, continuous glucose monitoring, hyperglycemia, glycemic excursions, early clinical studies

Continuous glucose monitoring (CGM) technology is a minimally invasive method of measuring glucose levels in real time over several days. It consists of an implanted device with a tiny sensor inserted just below the surface of the skin to gain access to interstitial fluid. An algorithm incorporating 3 to 4 capillary blood glucose measurements sampled by fingerstick for calibration is used to convert the interstitial glucose to blood glucose levels. The readout is a blood glucose profile with measurements taken every 5 minutes. This groundbreaking technology has advanced the management of diabetes mellitus by facilitating the use of insulin pumps, closed-loop systems, and the artificial pancreas.[1] CGM permits thorough examination of glycemic events such as hypoglycemic (<70 mg/dL) and hyperglycemic (>250 mg/dL) episodes, which can be life threatening and/or lead to severe complications. [2–5] It can also expose potential root causes for these excursions by linking changes in glycemic variability to medication, physical activity, diet/food intake, or other stresses. These observations can, in turn, help patients and practitioners develop strategies to correct and avoid future glucose extremes. Several studies have shown that the use of CGM devices also improves overall glucose control and can lower long-term hemoglobin A_{1c} (HbA_{1c}) in diabetes mellitus patients through greater glycemic awareness (see reviews[6,7]). These findings were recently confirmed in the DIAMOND trial, in which 24 weeks of CGM therapy improved glycemic control in both type 1[8] and type 2[9] diabetes mellitus patients on multiple daily insulin injections. Moreover, the American Association of Clinical Endocrinologists recommends CGM for patients at risk of hypoglycemia, T2DM patients with unappreciated hyperglycemia, and individuals using intensive insulin therapy regardless of diabetes type.[10,11] The US Food and Drug

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Submitted for publication 8 September 2017; accepted 8 December 2017.

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Administration recently granted the use of a CGM device to replace fingerstick self-monitoring blood glucose (SMBG) measurements for treatment decisions (ie, daily insulin dose).[12]

Although CGM can improve the lives of both type 1 and type 2 diabetes mellitus patients, another area benefiting from CGM technology is therapeutic drug development. Incorporating CGM in early clinical studies can assist both in understanding if and how a new investigational product impacts glycemic control and in discerning the pharmacokinetic-pharmacodynamic relationship. This view was recently expressed in a joint statement by the European Association for the Study of Diabetes and the American Diabetes Association, which highlighted the supportive role CGM can play in clinical development for new insulin products and glucose-lowering agents for a diabetes mellitus indication.[13] One of the first reported applications of CGM in a therapeutic intervention was to monitor changes in glucose concentrations as a safety biomarker. CGM was used as a primary efficacy endpoint for measurement of nocturnal hypoglycemia in type 1 diabetes mellitus subjects using an insulin pump.[14] Despite it being recognized by regulatory authorities as a clinical study endpoint,[15] there are only a handful of registered-controlled drug trials that use CGM in the context of type 2 diabetes mellitus (T2DM). These trials include a head-to-head sitagliptin vs vildagliptin study[16]; during an insulin plus sitagliptin add-on therapy study,[17] and a proof-of-concept study for a new compound.[18] One obstacle to further use of this technology as a pharmacodynamic endpoint in drug development programs may be related to the lack of data on the daily variation in glucose concentrations observed in T2DM patients. CGM has been examined in numerous studies with type 1 diabetes mellitus patients, especially in association with new insulins, insulin pumps, and closed-loop systems.[1] However, this technology has not been widely described in the literature for clinical use in patients with T2DM,[18] particularly for T2DM patients not on insulin treatment. Therefore, we examined intrapatient and between-day variance of CGM during 48-hour measurements in patients with T2DM treated with metformin or changes in lifestyle only, a key consideration when implementing a pharmacodynamic assessment such as CGM into early clinical research studies.

Methods

Study Design

Adult male and female patients with T2DM, 18–70 years old, with body mass index (BMI) values between 28 and 42 kg/m^2 were included in a retrospective clinical study utilizing CGM. Patients were recruited from 4 clinical research units (CRUs) in a competitive enrollment study design. Patients on stable doses of metformin or on nonpharmacological diabetes mellitus management for at least 3 months were included in the study, and subjects on insulin or hypoglycemic agents other than metformin were excluded. Subjects were also excluded if they had a history of significant cardiovascular disease or other disorders. The study protocol was approved by the Chesapeake IRB (Columbia, Maryland) ethics research board, and written informed consent was obtained from each subject. The results were obtained from a subanalysis of a larger double-blind, placebo-controlled clinical study (NCT02377362). The current analysis includes a subset of 24 subjects at baseline (predose) with uninterrupted recordings over 2 days.

Continuous Glucose Monitoring

The Medtronic iPro2 continuous glucose monitoring system (Dublin, Ireland) consists of the iPro2 recorder and an implanted glucose sensor. The glucose sensor was applied to the subject's abdomen according to manufacturer's instructions. Briefly, the sensor was inserted just underneath the skin using the Sen-Serter, and the iPro2 recorder unit was attached to the sensor and adhered to the body with occlusive adhesive dressing. One hour after CGM implant placement, blood glucose was measured with a SMBG meter (MediSense Precision Xtra, Abbott, Chicago, Illinois) to provide a calibration value. The patients were released from the clinic and instructed to perform another SMBG measurement at least 3 hours after implantation and another before bedtime (on day -1). Over the next 2 subsequent days (days 1 and 2), patients were instructed to obtain 4 daily SMBG measurements (before each meal and before bedtime) for retrospective CGM data correction and calibration. All patients were advised to maintain their regular dietary and exercise habits during the study but to refrain from strenuous physical activity. The CGM device was worn for approximately 72 hours, at which point the patients returned to the clinic (day 3), and the iPro2 recorder and sensor were removed. The sensor captures glucose readings every 5 minutes, for a total of 288 data points collected per day. The data from the CGM and SMBG blood glucose meter were uploaded into the CareLink iPro software platform (Medtronic) and exported into Excel (Microsoft, Redmond, Washington). According to the manufacturer's instructions, a minimum of 2 calibration points is required after implantation. The start of CGM recordings per patient ranged from 08:40 to 21:50 hours on the day of device insertion (day -1). Consequently, for analysis purposes midnight (00:00 hours) was set as the start of day 1, and daily glucose was defined as midnight to midnight, as reported by others.[10] The device has a mean absolute relative difference of 15.6% compared to venous blood glucose reference standard of measurement.

Table 1. Demographic and Fasting Glycemic Values

Parameter	All	CRU 1	CRU 2	CRU 3	CRU 4
n	24	11	8	2	3
Sex (%male)	71%	73%	63%	50%	100%
Age (years)	51 ± 12	44 ± 10	59 ± 7	37 ± 7	61 ± 9
Ethnicity (%Hispanic)	71%	64%	63%	100%	100%
BMI (kg/m^2)	31.6 ± 3.3	30.6 ± 1.3	33.0 ± 3.4	36.3 ± 6.6	28.3 ± 0.3
HbA_{1c} (%)	8.3 ± 0.8	8.4 ± 1.0	8.3 ± 0.7	8.0 ± 0.5	7.9 ± 0.6
Glucose (mg/dL)	173.4 ± 41.3	178.7 ± 40.1	181.6 ± 48.2	128.0 ± 28.3	162.3 ± 18.6
Insulin (μU/mL)	18.9 ± 8.7[b]	20.5 ± 7.5[b]	16.4 ± 6.7	33.8 ± 3.2	11.9 ± 8.0
HOMA-IR[a]	8.17 ± 4.20[b]	9.35 ± 4.60[b]	7.66 ± 4.03	10.79 ± 3.39	5.02 ± 2.15

Data shown as means ± SD, unless otherwise indicated.
[a]Homeostatic model assessment for insulin resistance.
[b]Insulin determined from 20 subjects (7 subjects from CRU 1).

Statistical Analysis

Results are presented as 24-hour average ± SD and area under the curve (AUC). Mean weighted glucose was calculated as the AUC divided by 24. Insulin sensitivity was estimated with the homeostatic model assessment for insulin resistance (HOMA-IR), calculated as [glucose (mg/dL) × insulin (μU/mL)]/405.[19] HOMA-IR is a validated method to evaluate insulin sensitivity with fasting glucose and insulin values; insulin resistance is typically defined as HOMA-IR >2.0.[20,21] Pearson coefficient (R) and Bland-Altman tests were used to determine between-day reproducibility.[22,23] Daily differences were examined by paired Student t-test. Statistical significance was set at $P < .05$. Graphs and statistical analyses were performed using GraphPad Prism 7 (GraphPad Software, La Jolla, California) and Excel (Microsoft, Redmond, Washington).

Results

Twenty-four patients with T2DM were included in this study analysis, 11 from Celerion, Inc (Phoenix, Arizona), and the remaining 13 from partnering clinical research units, namely Clinical Pharmacology of Miami (Miami, Florida), Clinical Trials of Texas (San Antonio, Texas), and Profil (San Diego, California). Anthropometric and demographic results are shown in Table 1. Overall, the subjects were predominantly middle aged, overweight and obese Hispanic males. The 2 patients from CRU 3 were younger (32, 42 years) and had average fasting insulin levels that were 1.6- to 2.8-fold higher than values from patients from the other sites. In addition, these 2 patients also displayed a higher average BMI value (31.6, 41.0 kg/m^2) (Table 1). All remaining demographic parameters were similar among the clinical sites.

Examples of typical CGM profiles and the cohort average glucose concentrations are shown in Figure 1. The CGM recordings over 2 consecutive 24-hour periods were nearly superimposable, signifying good low daily variability. Indeed, the average glucose concentrations from day 1 and day 2 strongly correlated as determined by Pearson coefficient (Figure 2A) and Bland-Altman tests (Figure 2B). To further evaluate the daily variation, a number of common CGM metrics were calculated including glucose AUC and mean weighted glucose. These values were also extremely similar between the 2 study days as demonstrated by significant Pearson coefficient association (Table 2). In addition, the time a patient spent within a given glycemic range was also evaluated. Overall, individual glucose concentrations were within the 70–250 mg/dL glycemic range for approximately 75% of time (Table 2). Hyperglycemia, defined here as >250 mg/dL, occurred for approximately 20% of the time and was observed in the majority of patients: 20 patients on day 1 and 21 patients on day 2. The average maximal (±SD) glucose concentrations captured were 299.5 ± 57.6 mg/dL and 308.0 ± 57.4 mg/dL (P = NS) for day 1 and day 2, respectively. Low daily variability was observed for all ranges except for the percentage of time spent in hypoglycemia; however, this percentage of time was minimal (<1%, Table 2). Although the number of subjects from CRU 3 and CRU 4 were small, there did not appear to be a site or day effect for the average daily glucose levels (Figure 3).

For retrospective calibration of the CGM device, SMBG values must be captured several times a day. Patients were instructed to measure capillary blood glucose in the morning, afternoon, evening, and before bedtime (Figure 4). On day 1, average morning SMBG was 179.3 ± 33.9 mg/dL and increased by 8% in the afternoon and then by 25.2% before bedtime. A similar trend was observed on day 2 with an average morning SMBG value of 182.1 ± 40.6 mg/dL, which increased by 9.6%, 13.8%, and 21.5% in the afternoon, evening, and nighttime, respectively. Overall, fingerstick SMBG values were similar between days except for the evening measurement (176.1 ± 69.6 mg/dL and

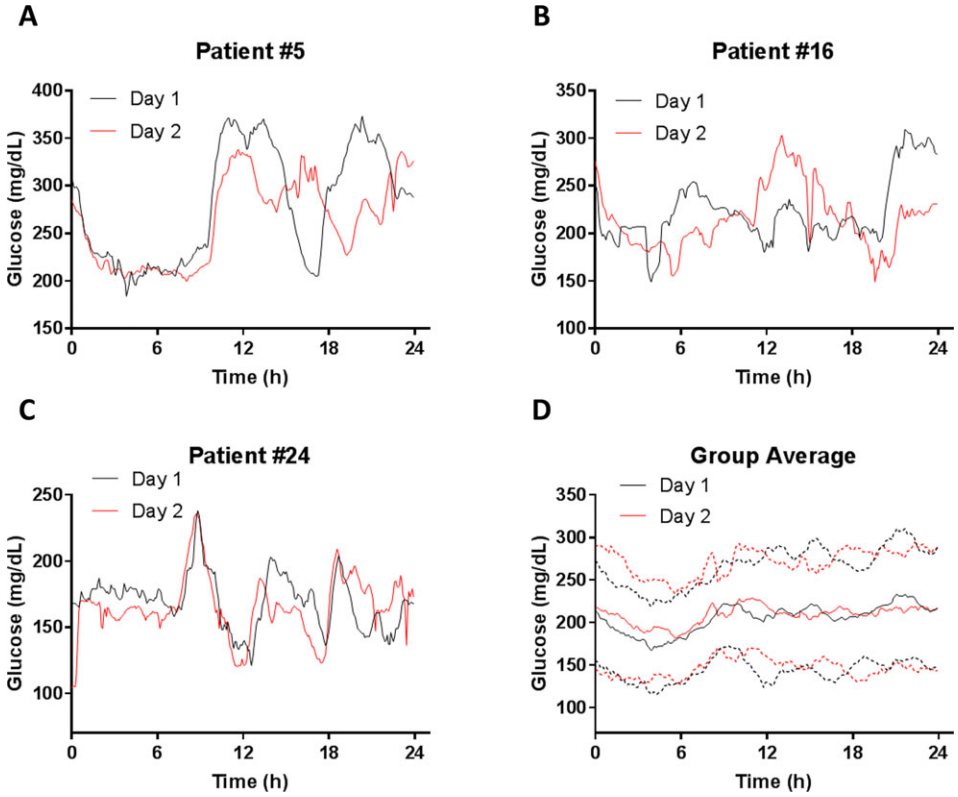

Figure 1. A-C, Glucose profiles of representative individual patients by day. D, Cohort average glucose concentration by day. Data are shown as average (solid lines) ± SD (dashed lines); with day 1 shown in black and day 2 in red.

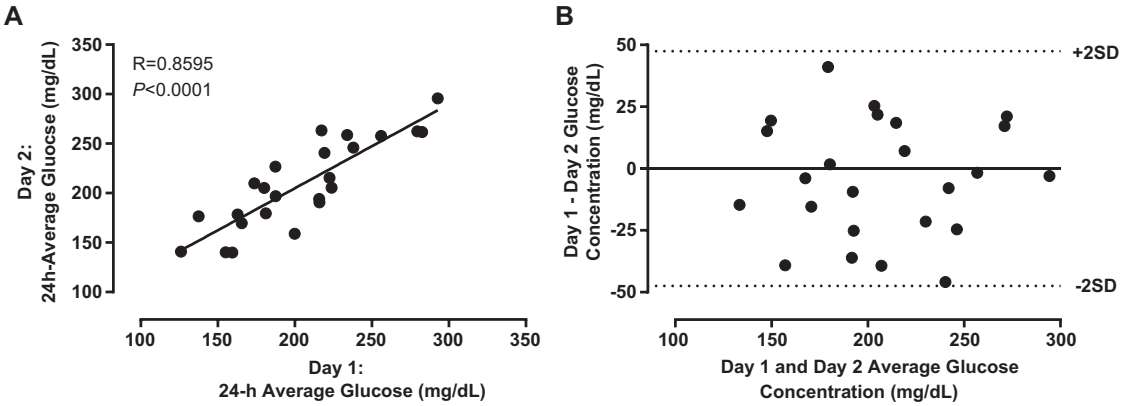

Figure 2. Variation assessment of 24-hour average glucose. A, Correlation between day 1 and day 2 average glucose concentration. The Pearson regression coefficient (R) and *P* value are presented. B, Bland-Altman analysis of daily average glucose. Dashed lines represent 2× the upper and lower SD.

207.3 ± 54.6 mg/dL, $P = .05$ for day 1 and day 2, respectively).

Discussion

The primary endpoint for many diabetes mellitus clinical studies is a reduction in HbA_{1c}. HbA_{1c} is a marker for long-term glucose control, as it is an indicator of the average blood glucose concentration over the previous 2–3 months. Although HbA_{1c} is considered the reference standard for examining long-standing glycemic control, it is not a suitable outcome measure for shorter trials, such as those in early clinical research (phase 1 and 2a studies). To this end, CGM can be a powerful endpoint for short-term, proof-of-principle or proof-of-mechanism studies. However, only a handful of studies have incorporated CGM into a T2DM trial. Therefore, we evaluated the daily subject variation in CGM measures from patients with T2DM across multiple centers in order to assess the robustness of this

Table 2. Continuous Glucose Monitoring Outcome Metrics

Parameter	Day 1	Day 2	Pearson R	*P* Value
Average 24-h glucose concentration (mg/dL)	204.8 ± 45.0	208.9 ± 44.5	0.8595	<.001
%CV	21.98%	21.29%		
Area under the curve (mg·h/dL)	4897.3 ± 1076.1	4995.0 ± 1061.7	0.8624	<.001
Mean-weighted glucose (mg/dL)	204.1 ± 44.8	208.1 ± 44.2	0.8624	<.001
Patient percentage time in ranges (%):				
<70 mg/dL	0.7 ± 2.2	0.4 ± 1.7	0.3223	.1336
70-180 mg/dL	36.3 ± 33.8	36.0 ± 30.3	0.7366	<.001
181-250 mg/dL	41.7 ± 24.7	39.0 ± 17.8	0.5509	.006
>250 mg/dL	21.0 ± 21.4	24.6 ± 24.4	0.8931	<.001

Data shown as means ± SD, unless otherwise indicated. %CV was calculated for average 24-hour daily glucose.

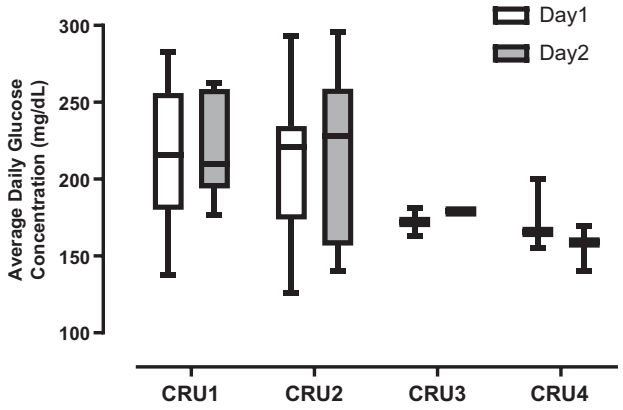

Figure 3. Comparison of between-site CGM glucose concentrations: 24-hour average glucose on day 1 and day 2 presented by clinical research site. Data are presented as a box plot: the center line represents the median, the bottom and top lines are the 25th and 75th percentiles, and the ends of the whiskers are the 5th and 95th percentiles, respectively. CGM indicates continuous glucose monitoring.

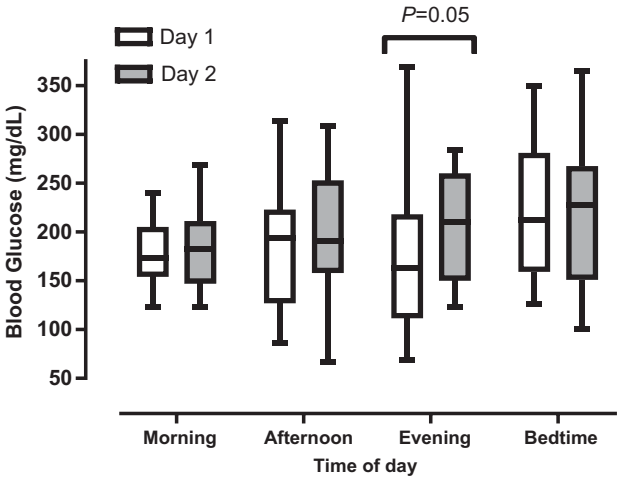

Figure 4. Self-monitoring blood glucose (SMBG) values. Capillary fingerstick glucose values for CGM calibration taken over the course of day 1 and day 2. Data presented as a box plot: the center line represents the median, the bottom and top lines are the 25th and 75th percentiles, and the ends of the whiskers are the 5th and 95th percentiles, respectively. CGM indicates continuous glucose monitoring.

technology for use in clinical studies. The present study demonstrated robust between-day reproducibility of CGM from 24 patients using different statistical assessments. These findings are in line with previously published results showing good accuracy and strong sensitivity and specificity for CGM.[6,18]

To our knowledge this is the first study to examine daily variation in a T2DM cohort and report reference values for a primarily Hispanic population. These values can be applied to power calculations for future clinical studies. Others have demonstrated that 24-hour mean blood glucose and measures of glycemic excursions were similar in a healthy Chinese cohort during a test-retest study with a 3-day CGM evaluation.[24,25] There are a number of limitations that must be addressed. Since this was a retrospective study with competitive enrollment, it was not possible to control for the number of patients included by each clinical site, which precludes a detailed intersite analysis. Even so, mean HbA_{1c}, fasting glucose, and average daily glucose concentrations were similar among the research centers. Another study limitation is related to meals and physical activity. As patients were not confined to the clinic during the CGM assessment, meals and physical activity levels may not have been identical between days. Nonetheless, this allowed to assess daily glucose variation under normal living conditions. Although the glucose profiles were extremely similar, they were not anticipated to be completely superimposable. Previous studies have highlighted the effect of a meal on CGM glucose responses; Chlup et al demonstrated the duration and magnitude of glycemic response to various foods (eg, honey, dark chocolate, white bread) with a fixed amount of carbohydrates (50 g) can be

dramatically different.[26] In addition, in a controlled setting, Zhou et al observed 10% and 14% rises in blood glucose 1 hour after meal consumption at lunch and dinner (50% of macronutrients from carbohydrates), respectively, but no breakfast effect.[24] Given the influence of meals on a glucose profile, and the assumption that meals were not similar between study days, the daily variation when taken as 24-hour average remains highly reproducible.

Regardless of diabetes mellitus type, the American Diabetes Association Standards of Care guidelines indicate that GCM is a useful tool to promote greater hypoglycemia awareness and disease management.[27] Another key advantage of the CGM system is the ability to capture previously undiagnosed hyperglycemia, a finding often missed by SMBG sampling. In the present study nearly all subjects reported some time in the hyperglycemic range by CGM, yet only 10 and 14 patients demonstrated glucose levels >250 mg/dL by SMBG on days 1 and 2, respectively. This finding is similar to the results obtained by Kohnert et al who observed that well-controlled T2DM patients (HbA_{1c} <7.0%) spent an average of 5.7 h/d in the hyperglycemic range and experienced 4.1 episodes of hyperglycemia per day.[28] Therefore, glucose fluctuations captured by CGM are more powerful in detecting hyperglycemia than SMBG or HbA_{1c} alone. As a clinical study endpoint, changes in CGM metrics related to hyperglycemia have the potential to demonstrate clinical benefit.

With a wealth of acquired data points, there are a number of ways to analyze and present CGM results. Historically, typical assessments include 24-hour average, mean weighted average, AUC, and percentage time in ranges as well as assessment of glycemic excursions through SD, mean amplitude of glucose excursion, or continuous overlapping net glycemic action.[29] In addition, for interventional studies, time to maximum glucose concentration and change in daily average glucose are also common endpoints. With numerous CGM outcome measures, interpretation of the results can be challenging for patients, physicians, and researchers. Therefore, in an effort to form a consensus on reporting CGM results, the American Association of Clinical Endocrinologists, and American College of Endocrinology recommend standardization of outcome metrics. The goal is to develop reports that are as universally comprehensible by clinicians as an electrocardiogram.[7] These measures include percentage time in ranges, glycemic variability reported as SD (or %CV), average daily glucose, and estimated HbA_{1c}.[7] The present study demonstrated robust reproducibility between days for several of these metrics in a T2DM cohort.

In the present multisite study data showed minimal glucose variation among all study participants, confirming suitability for early clinical research. Furthermore, CGM can support pharmacovigilance; the number of hypoglycemia events and time spent in hypoglycemic range were evaluated in a phase 2 study comparing an investigational pegylated basal insulin (insulin peglispro [LY2605541]) to insulin glargine in T2DM subjects.[30] Moreover, when baseline medication is withheld from T2DM subjects during phase 2 monotherapy studies, risk of hyperglycemia can be closely monitored by CGM. CGM may also be a valuable safety consideration for other indications, such as polycystic ovary syndrome, cystic fibrosis, thalassemia major, acute coronary syndrome, and renal impairment,[31] where risk of glucose variability is high and/or diabetes mellitus is a comorbidity. Therefore, from a drug development program perspective, CGM is to glucose measurements as Holter monitors are to electrocardiograms.[18]

Conclusion

Frequent readings every 5 minutes provide a CGM glucose profile over the course of the day, and despite changes in response to daily activities such as eating, sleeping, and physical activity, the results demonstrated low daily variability. This is an important consideration when implementing new technology into therapeutic intervention programs, as the ability to demonstrate minimal daily variation with placebo or baseline treatments will allow for a better evaluation of pharmacodynamic effects. Altogether, the results from the present study indicated that there is strong between-day reproducibility in CGM in a T2DM cohort and demonstrated that this method is practical for multisite studies. As a Food and Drug Administration– and European Medicines Authority–recognized clinical endpoint, CGM is a powerful pharmacodynamic tool for drug efficacy and safety monitoring that can contribute to improving and accelerating drug development programs.

Declarations

S.P. and B.H.M. are employees of Celerion. A.d.l.P. is an employee and minor shareholder of Eli Lilly and company, Chorus division. C.F. is the CEO of GLWL Research Inc.

The authors would like to acknowledge the collaboration of our partnered clinical research units, Clinical Trials of Texas (San Antonio, TX), Profil (San Diego, CA), and Clinical Pharmacology of Miami (Miami, FL); and the outstanding work from the Celerion clinical team. We would also like to thank Katherine "Shelly" Dunnington and Peng Chai from Celerion for assistance with manuscript preparation and all the subjects for participating in this study.

References

1. Thabit H, Hovorka R. Coming of age: the artificial pancreas for type 1 diabetes. *Diabetologia*. 2016;59(9):1795–1805.
2. Cryer PE. The barrier of hypoglycemia in diabetes. *Diabetes*. 2008;57(12):3169–3176.
3. Papanas N, Ziegler D. Risk factors and comorbidities in diabetic neuropathy: an update 2015. *Rev Diabet Stud.* 2015;12(1–2):48–62.
4. Palsson R, Patel UD. Cardiovascular complications of diabetic kidney disease. *Adv Chronic Kidney Dis.* 2014;21(3):273–280.
5. Chen R, Ovbiagele B, Feng W. Diabetes and stroke: epidemiology, pathophysiology, pharmaceuticals and outcomes. *Am J Med Sci.* 2016;351(4):380–386.
6. Mamkin I, Ten S, Bhandari S, Ramchandani N. Real-time continuous glucose monitoring in the clinical setting: the good, the bad, and the practical. *J Diabetes Sci Technol.* 2008;2(5):882–889.
7. Fonseca VA, Grunberger G, Anhalt H, et al. Continuous glucose monitoring: a consensus conference of the American Association of Clinical Endocrinologists and American College of Endocrinology. *Endocr Pract.* 2016;22(8):1008–1021.
8. 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(4):371–378.
9. 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(6):365–374.
10. Carlson AL, Mullen DM, Bergenstal RM. Clinical use of continuous glucose monitoring in adults with type 2 diabetes. *Diabetes Technol Ther.* 2017;19(S2):S4–S11.
11. Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm—2016 executive summary. *Endocr Pract*. 2016;22(1):84–113.
12. FDA expands indication for continuous glucose monitoring system, first to replace fingerstick testing for diabetes treatment decisions. 2016; Food and Drug Administration:https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm534056.htm. Accessed May 23, 2017.
13. Petrie JR, Peters AL, Bergenstal RM, Holl RW, Fleming GA, Heinemann L. Improving the clinical value and utility of CGM systems: issues and recommendations: a joint statement of the European Association for the Study of Diabetes and the American Diabetes Association Diabetes Technology Working Group. *Diabetes Care*. 2017;40(12):1614–1621. https://doi.org/10.2337/dci17-0043.
14. Bergenstal RM, Klonoff DC, Garg SK, et al. Threshold-based insulin-pump interruption for reduction of hypoglycemia. *N Engl J Med.* 2013;369(3):224–232.
15. Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus 2012; European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP). http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129256.pdf. Accessed May 23, 2017.
16. Marfella R, Barbieri M, Grella R, Rizzo MR, Nicoletti GF, Paolisso G. Effects of vildagliptin twice daily vs. sitagliptin once daily on 24-hour acute glucose fluctuations. *J Diabetes Complications*. 2010;24(2):79–83.
17. Koyanagawa N, Miyoshi H, Ono K, et al. Comparative effects of vildagliptin and sitagliptin determined by continuous glucose monitoring in patients with type 2 diabetes mellitus. *Endocr J.* 2016;63(8):747–753.
18. Vigersky R, Shrivastav M. Role of continuous glucose monitoring for type 2 in diabetes management and research. *J Diabetes Complications*. 2017;31(1):280–287.
19. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985;28(7):412–419.
20. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. *Diabetes Care*. 2004;27(6):1487–1495.
21. Gayoso-Diz P, Otero-Gonzalez A, Rodriguez-Alvarez MX, et al. Insulin resistance (HOMA-IR) cut-off values and the metabolic syndrome in a general adult population: effect of gender and age: EPIRCE cross-sectional study. *BMC Endocr Disord.* 2013;13:47.
22. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet.* 1986;1(8476):307–310.
23. Bland JM, Altman DG. Measurement error and correlation coefficients. *BMJ*. 1996;313(7048):41–42.
24. Zhou J, Li H, Ran X, et al. Reference values for continuous glucose monitoring in Chinese subjects. *Diabetes Care*. 2009;32(7):1188–1193.
25. Zhou J, Li H, Ran X, et al. Establishment of normal reference ranges for glycemic variability in Chinese subjects using continuous glucose monitoring. *Med Sci Monit.* 2011;17(1):CR9–CR13.
26. Chlup R, Peterson K, Zapletalova J, Kudlova P, Seckar P. Extended prandial glycemic profiles of foods as assessed using continuous glucose monitoring enhance the power of the 120-minute glycemic index. *J Diabetes Sci Technol.* 2010;4(3):615–624.

27. American Diabetes Association. Glycemic targets. Sec. 6. In Standards of Medicinal Care in Diabetes—2017. *Diabetes Care*. 2017;40(Suppl. 1):S48–S56.
28. Kohnert KD, Augstein P, Heinke P, et al. Chronic hyperglycemia but not glucose variability determines HbA_{1c} levels in well-controlled patients with type 2 diabetes. *Diabetes Res Clin Pract.* 2007;77(3):420–426.
29. Jung HS. Clinical implications of glucose variability: chronic complications of diabetes. *Endocrinol Metab (Seoul)*. 2015;30(2):167–174.
30. Bergenstal RM, Rosenstock J, Bastyr EJ 3rd, Prince MJ, Qu Y, Jacober SJ. Lower glucose variability and hypoglycemia measured by continuous glucose monitoring with novel long-acting insulin LY2605541 versus insulin glargine. *Diabetes Care*. 2014;37(3):659–665.
31. Soliman A, DeSanctis V, Yassin M, Elalaily R, Eldarsy NE. Continuous glucose monitoring system and new era of early diagnosis of diabetes in high risk groups. *Indian J Endocrinol Metab.* 2014;18(3):274–282.