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Clinical Accuracy of a Continuous Glucose Monitoring System With an Advanced Algorithm

Timothy S. Bailey, MD[1], Anna Chang, MD[2], and Mark Christiansen, MD[3]

Abstract

We assessed the performance of a modified Dexcom G4 Platinum system with an advanced algorithm, in comparison with frequent venous samples measured on a laboratory reference (YSI) during a clinic session and in comparison to self-monitored blood glucose (SMBG) during home use. Fifty-one subjects with diabetes were enrolled in a prospective multicenter study. Subjects wore 1 sensor for 7-day use and participated in one 12-hour in-clinic session on day 1, 4, or 7 to collect YSI reference venous glucose every 15 minutes and capillary SMBG test every 30 minutes. Carbohydrate consumption and insulin dosing and timing were manipulated to obtain data in low and high glucose ranges. In comparison with the laboratory reference method (n = 2,263) the system provided a mean and median absolute relative differences (ARD) of 9.0% and 7.0%, respectively. The mean absolute difference for CGM was 6.4 mg/dL when the YSIs were within hypoglycemia ranges (≤ 70 mg/dL). The percentage in the clinically accurate Clarke error grid A zone was 92.4% and in the benign error B zone was 7.1%. Majority of the sensors (73%) had an aggregated MARD in reference to YSI ≤ 10%. The MARD of CGM-SMBG for home use was 11.3%. The study showed that the point and rate accuracy, clinical accuracy, reliability, and consistency over the duration of wear and across glycemic ranges were superior to current commercial real-time CGM systems. The performance of this CGM is reaching that of a self-monitoring blood glucose meter in real use environment.

Keywords

clinical accuracy, continuous glucose monitoring, advanced algorithm

Since the advent of continuous glucose monitoring, researchers and clinicians have questioned whether CGM accuracy was adequate to be used routinely in clinical practice. Mazze et al, after evaluating the Dexcom STS CGM system and the Medtronic Guardian CGM systems, concluded that there was "sufficient incongruence between simultaneous blood glucose levels and interstitial fluid glucose to question the fundamental assumption that interstitial glucose and blood glucose could be made identical by resorting to algorithms based on concurrent blood glucose levels alone."[1] In a publication discussing methods to assess and compare CGM systems, Wentholt et al stated that the accuracy of current sensors "is in need of substantial improvement."[2] Hermanides et al, hypothesized in an argument against CGM that physiologic and instrument delay, inherent to the current real-time CGMs, contribute to the inaccuracies of the devices.[3] Other studies have reported significant inaccuracies and the poor CGM performance and that the inaccuracies contributed to lack of observed glycemic benefit or lack of perseverance with CGM use.[4-6] Because of imprecision of historical products and resulting safety concerns, CGM systems to date have received regulatory approval in the United States only for use adjunctive to self-monitored blood glucose (SMBG).

The Dexcom G4 Platinum was a major step forward in improving the performance of CGM. In the pivotal study, the overall accuracy, accuracy in the critical low glucose range, accuracy over time, precision, and reliability were all improved compared to the Dexcom Seven Plus, the previous-generation Dexcom CGM.[7] These performance improvements were confirmed in independent assessments.[8-11]

Further improvements were thought needed to meet the stringent requirements of an artificial pancreas system. Accordingly, collaboration between an academic research group from University of Padova and Dexcom resulted in updated noise reduction and a modified calibration algorithm. More details of some of the algorithm changes and a simulation of the performance of the new algorithm were

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previously published.[12] They found that the algorithm resulted in a reduction in signal-processing-induced time delays and that performance was improved on the first day of use and at low plasma glucose in simulation environments.

The purpose of this clinical study was to assess the accuracy and reliability of the new algorithm, used in a modified Dexcom G4 Platinum receiver, in comparison with frequent venous samples measured on a laboratory reference system during a clinic session and in comparison to SMBG during home use. This CGM system includes the same sensor and transmitter as the Dexcom G4 Platinum but has a modified receiver, containing the new algorithm.

Study Design

The modified CGM system was tested in an open-label, single-arm, multicenter clinical study involving subjects 18 years of age or older with type 1 and type 2 diabetes using multiple daily injections or insulin pumps. Subjects were excluded if they had hematocrits outside the range of the study blood glucose meter, were pregnant or on dialysis, required acetaminophen, had a condition such as cardiovascular or cerebrovascular disease, epilepsy, or significant hypoglycemia unawareness that would pose a risk from inducing hypoglycemia as required in the protocol, had a recent severe hypoglycemia event, or had a chronic infectious disease that could pose a risk to the study staff handling blood samples.

Study Procedures and Data Collection

After self-training using a tutorial or 1-on-1 training, subjects self-inserted their own sensor (they used a single system) in the subcutaneous tissue of their abdomen. Subjects were instructed to calibrate their receiver twice daily per current labeling recommendation. All subjects used the Bayer Contour Next USB meter for calibration of the CGM device and for routine blood glucose testing; multiple test strips lots were utilized during the study. Subjects were asked to come to the clinic on day 1, 4, or 7 for a 12-hour session for comparison of CGM readings to both venous and capillary glucose. During their clinic session, subjects had venous blood draws approximately once every 15 ± 5 minutes for measurement on the YSI (Yellow Springs, OH) blood glucose analyzer and fingerstick SMBG every 30 ± 5 minutes for capillary glucose measurements using a Bayer USB Next meter. The venous samples were arterialized with a heating pad at the venous sample catheter site. Additional SMBG measurements were obtained as needed for diabetes management. Meals, insulin dose amounts, and insulin dose timing were manipulated per protocol during the clinic session to obtain a wide range of glucose values; for example, insulin administration was held for up to 90 minutes after a meal, and no correctional component was included in the meal insulin dose to obtain high glucose; and the glucose target used to determine the correctional component of the insulin dose was adjusted to 60 mg/dl to obtain low glucose. The CGM display was blinded during the clinic session. During home use, the CGM data were displayed; however, subjects were instructed to manage their glucose level as per their routine diabetes management guidelines based on their SMBG measurements. The study protocol was reviewed by the FDA through the Investigational Device Exemption process and approved by an institutional review board. All subjects provided witnessed, written informed consent prior to enrollment. The study was registered at clinicaltrial.gov (NCT# NCT02087995).

Statistical Methods and Data Analysis

CGM performance was assessed by comparing the CGM glucose with the immediate temporally prospective matched (closest in time) YSI glucose or SMBG.

Pearson correlation coefficients were used to evaluate the relationships between CGM, YSI, and SMBG measurements. The CGM performance was evaluated in absolute relative differences (%), determined as an aggregate value from the total number of paired points compared with the reference value. The mean ARD was also assessed individually for each sensor in the study and plotted as a histogram distribution. The mean absolute difference (MAD; in mg/dL) was used to assess accuracy when blood glucose was less than or equal to 70 mg/dL. The performance evaluation included the proportion of the CGM system values that are within ±20% of relative difference of reference value at glucose levels >80 mg/dL and ±20 mg/dL of absolute difference at glucose level ≤ 80 mg/dL (hereafter referred to as % 20/20) as well the proportion of the CGM system values that are within ± 30% of relative difference of reference value at glucose levels >80 mg/dL and ±30 mg/dL of absolute difference at glucose level ≤ 80 mg/dL (hereafter referred to as % 30/30).

Clarke error grid (CEG) analysis[13] was used to quantify the clinical accuracy of CGM in reference to the laboratory standard of YSI. Diagnostic features of the CGM were assessed in hypoglycemia and hyperglycemia detection rates, which show how often the device recognizes and alerts the patient to a low or high glucose event or how often it misses an event, as well as CGM alert rates, which show how often the device alert is correct (the reference glucose is also at low or high levels) or incorrect. Time lag between venous YSI and interstitial fluid CGM glucose was estimated as the time shift that resulted the optimal correlation coefficient derived from two glucose curves during the clinic session.[14]

The CGM performance during home use was quantified in reference to the SMBG, using the assessment performed in the comparison to the YSI reference. The overall CGM reliability was evaluated by comparing the number of sensor measurements per day relative to the maximum possible readings per day. Sensor life was also evaluated as the time from the first CGM reading after insertion to the time of sensor failure prior to the removal.

Summary statistics for continuous variables include mean, standard deviation, median, and range. Categorical variables are presented as counts and percentages. Histogram and density modified Bland–Altman plots were used to depict the data distribution and bias between CGM and the references. All analyses were performed using SAS® software, version 9.1.3 or later (SAS Institute, Inc, Cary, NC). Chi-square tests were used for comparisons of categorical variables, and nonparametric tests were used for comparisons of continuous variables. All hypothesis tests were carried out at the 5% significance level.

Results

Study Population

Fifty-one subjects enrolled in this prospective study performed at 3 sites in the United States. Subjects were 46.7 ± 15.8 (mean ± SD) years old, ranging 20 to 86 years of age, and 24 (47%) were women. Subjects had a diagnosis of diabetes for 24.8 ± 14.5 years; 44 (86%) had T1DM, and 7 (14%) had T2DM. Twenty-seven (53%) were on continuous subcutaneous insulin infusion (CSII) pumps, and 24 (47%) delivered insulin via multiple daily injections (MDI). Average body mass index was 27.4 ± 4.6 kg/m^2, ranging from 20.1 to 39.0 kg/m2, and mean HbA1c was 7.8 ± 1.1%, ranging from 5.8% to 10.9% at baseline.

CGM Performance

During clinic evaluation, there were 2263 CGM readings that had a corresponding (temporally matched) reference YSI, and all of these matched pairs were included in the data analysis. The overall median ARD was 7.0% and the mean ARD was 9.0% between the CGM and YSI reference glucose. The average differences were better after the first day of wear (10.7%, 8.0% and 8.5% for day 1, day 4, and day 7, respectively). The CEG results showed that 92.4% of points fell in the clinically accurate A zone, with 99.5% of all points falling in the A and B zones. The corresponding clinically accurate A zones were similar at 92.9% in both hypoglycemia ranges (40 to 80 mg/dL) and hyperglycemia (>180 mg/dL) ranges. In addition, the Pearson correlation coefficient calculated between CGM and YSI measurements was .97, a statistically significant linear relationship ($P < .0001$). The % 20/20 was 93% and the % 30/30 was 98%.

Similar but slightly inferior performance was observed between CGM-SMBG matched pairs (Table 1). Using SMBG reference for comparison during home use, out of 2992 matched CGM-SMBG pairs, the overall median ARD was 9.0% and the mean ARD was 11.2%. There average differences were also slightly better after the first day (12.7%, 10.9%, and 9.9% for day 1, day 4, and day 7, respectively). There were no accuracy differences observed between day and night (8 PM to 8 AM) time (mean ARD of 11.1% vs 11.7%, $P = .19$, respectively).

Table 1. CGM Performance During Clinic and at Home.

Performance parameters	CGM vs YSI	CGM vs SMBG
Temporally matched pairs (N)	2263	2992
Pearson correlation coefficient	.97	.98
Mean absolute relative difference (ARD) (%)	9.0	11.3
% 20/20 / % 30/30	93.0 / 98.0	86.6 / 95.8
Mean ARD within day 1 / day 4 / day 7 (%)	10.7 / 8.0 / 8.5	12.2 / 10.1 / 9.7
Mean absolute difference (MAD) at hypoglycemia BG < = 70 mg/dl / (n)	6.4 mg/dL / (252)	7.9 mg/dL / (337)
Mean ARD at euglycemia 70 < BG < = 180 (%) / (n)	9.7 / (851)	11.6 / (1494)
Mean ARD at hyperglycemia BG > 180 mg/dl (%) / (n)	8.0 / (1160)	10.1 / (1161)
Overall CEG A + B zones / A zone (%)	99.5 / 92.4	98.9 / 85.4

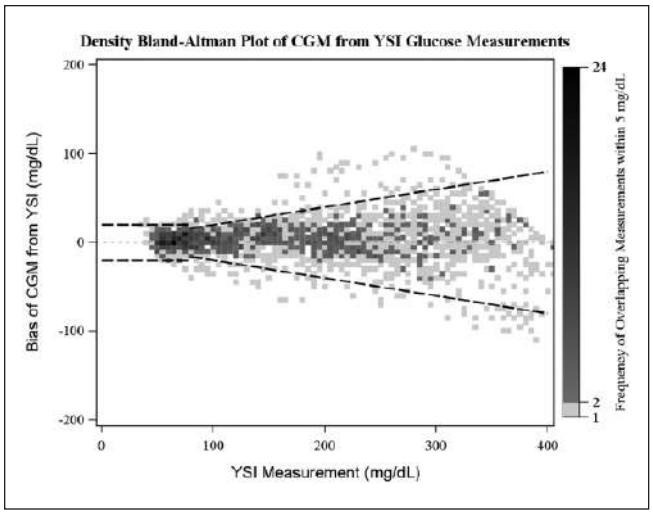

Figure 1. Density Bland–Altman bias plots of CGM-YSI.

The bias (mg/dL) of CGM to YSI and CGM to SMBG is illustrated in the density modified Bland–Altman plots (Figure 1 and Figure 2). These graphs demonstrate that the bias was centered around zero with high density (frequency). The majority of bias fell within the modified ISO boundaries (% 20/20). The performance of individual sensors is illustrated in Figure 3, the aggregated sensor mean ARD of CGM-YSI distribution. The histogram plot indicated that there were very few outlier sensors: 1 (2%) sensor had a sensor MARD greater than 20% (occurred on day 1), and 3 (6%) sensors had sensor MARDs greater than 15% (2 occurred on day 1, 1 occurred on day 7); 50% of sensors had MARDs less than 8%, and 75% of sensors had MARDs less than 11% with a mean of 9% and a standard deviation of 4%.

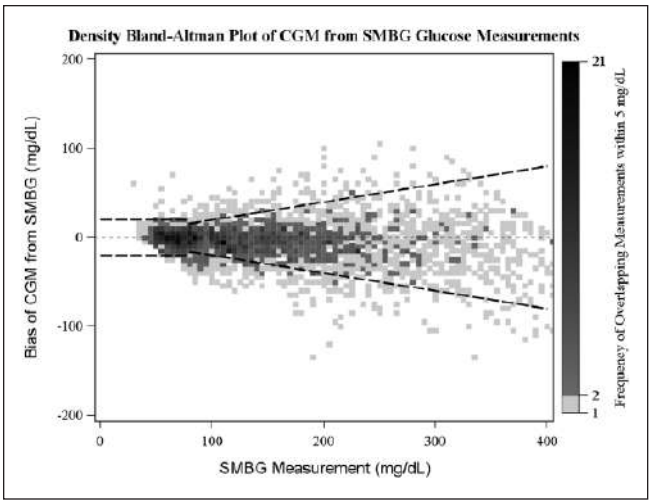

Figure 2. Density Bland–Altman bias plots of CGM-SMBG.

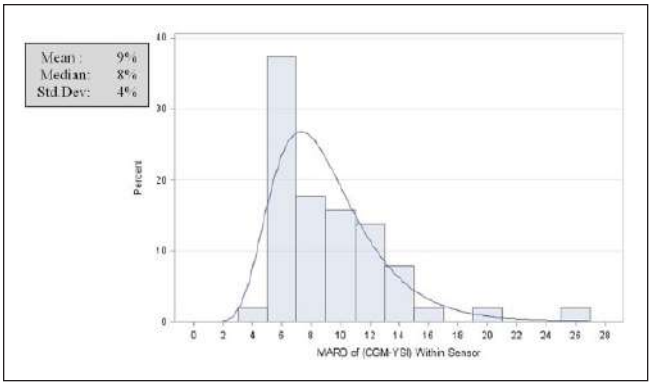

Figure 3. Aggregated sensor MARD (%) of CGM-YSI histogram plot. A log-normal density curve is overlaid on the histogram bars.

Hypoglycemina and Hyperglycemia Detection and CGM Threshold Alert Rate

When the threshold low glucose alert was set at 70 mg/dL, the CGM system detected true hypoglycemia (in YSI blood glucose measurement ≤ 70 mg/dL) 91% of the time within 15 minutes, and alerted correctly 92% of the time within a 15-minute time window with a 8% false alert rate. When the threshold high glucose alert was set a 200 mg/dL, the G4 Platinum detected true hyperglycemia (in YSI blood glucose measurement ≥ 200 mg/dL) 98% of the time within 15 minutes, and alerted correctly 96% of the time within a 15-minute time window with a 4% false alert rate.; when the threshold high glucose alert was set a 180 mg/dL, the CGM detected true hyperglycemia (in YSI blood glucose measurement ≥ 180 mg/dL) 99% of the time within 15 minutes, and alerted correctly 97% of the time within a 15-minute time window with a 3% false alert rate. Table 2 shows the hypoglycemia and hyperglycemia detection and true alert rates at commonly used threshold alert settings.

Table 2. Hypoglycemia/Hyperglycemia Detection and Alert Rates.

Threshold level (mg/dL)	Evaluable events (n)	Subjects having event	Hypoglycemia detection rate (95% CI) (%)	True alert rate (95% CI) (%)
70	260	43	91 (88, 95)	92 (90, 94)
80	386	47	90 (87, 93)	95 (93, 96)
90	477	48	94 (92, 96)	96 (95, 97)

Threshold level (mg/dL)	Evaluable events (n)	Subjects having event	Hyperglycemia detection rate (95% CI) (%)	True alert rate (95% CI) (%)
180	1206	49	99 (98, 99)	97 (96, 97)
200	1068	49	98 (97, 99)	96 (95, 96)
220	906	49	98 (97, 99)	94 (93, 95)
240	772	49	95 (94, 97)	93 (92, 94)

Sensor Stability and Reliability

Of the sensors, 94% (50 out of 51) lasted until study day 7. During a 7-day session, out of a maximum of 1992 glucose readings expected, 95% of the devices used in this study provided more than 75% CGM readings. On average, the CGM system provided an average of 97% of all expected CGM readings each day. The time lag of the interstitial fluid sensor was estimated as 5 to 6 minutes using maximum correlation coefficient statistics.

Safety Assessment

No serious adverse events or device-related serious adverse events occurred during the study. Mild skin irritation, such as erythema or edema, occurred in very low frequency around the adhesive area. No infection, bruising, or bleeding occurred at the sensor needle insertion area or the adhesive areas.

Discussion

This study confirms the marked improvement in CGM performance resulting from the algorithm modifications previously observed in the simulation by Garcia et al.[12] These improvements should have tangible benefits to CGM users. Although the direction and rate of glucose change are important and used by patients in their diabetes management, the point accuracy of the CGM is critical to a user's CGM experience.[15,16] When the CGM and expected glucose are discordant, based on their symptoms or in comparison to a SMBG, a user will be less likely to use the CGM data and may be less likely to persevere with CGM.[17]

The accuracy of this system, using twice a day calibrations, is much better than any system that has been marketed and is the first to have a mean ARD of smaller than 10%.

The accuracy reported for current systems is a mean ARD of 13.3% for Dexcom G4 Platinum, 14.9% for Medtronic 530 G with Enlite sensor calibrating every 12 hours, and 14.0% with Enlite sensor calibrating 3-4 time a day.[7,18] In fact, the point accuracy demonstrated in this study now exceeds the accuracy observed with some current blood glucose monitoring systems.[19-22]

The performance of the new system in the hypoglycemia range and minimal lag delay contribute to higher true alerts and hypoglycemia detection rates. The low false positive alerts should help avoid alert fatigue, and the high true positive and true negative alert rate should enhance user confidence in their CGM.[23] Whether this translates into better outcomes, such as greater reduction in severe hypoglycemia, requires further study.

The system was found to be reliable and there was consistent performance over the days of wear. There was no significant difference in accuracy between day or night use. Most users should have a positive experience with the system, as in this study few individuals had poorly performing sensors. This study highlights the importance of an algorithm for CGM performance. The algorithm utilized in this system, developed in collaboration between an academic center and industry, resulted in greater CGM performance improvements.

The Dexcom G4 Platinum was modified with the addition of a novel algorithm in the receiver, and this CGM system was studied in a clinical evaluation that included both in-clinic and home use. The study found an overall mean ARD of 9% and 8% after the first day of use compared to YSI reference. Very few (2%) of CGM-YSI matched pairs were outside of % 30/30 boundaries, and the majority of the sensors (37 out of 51, 73%) had MARDs less than and equal to 10%.[24] With the new algorithm, the Dexcom G4 Platinum system surpasses currently available CGM technologies in terms of accuracy and reliability. Clinical trials are needed to determine if the congruence to blood glucose reference values is sufficient to allow safe diabetes management and insulin dosing decisions based solely on CGM data.

Abbreviations

ADA, American Diabetes Association; ARD, absolute relative difference; A1c, hemoglobin A1c; CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion (insulin pump); SMBG, self-monitored blood glucose; MDI, multiple daily injections; T1D, type 1 diabetes mellitus; T2D, type 2 diabetes mellitus; YSI, Yellow Springs Instrument.

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Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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