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Multicenter Evaluation Study Comparing a New Factory-Calibrated Real-Time Continuous Glucose Monitoring System to Existing Flash Glucose Monitoring System

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Abstract

This study reports a clinical evaluation of AiDEX CGM system featuring a 14-day sensor, real-time glucose monitoring and factory-calibration. A multicenter, prospective, masked clinical study was conducted at with a total of 120 participants. Each participant wore 4 studied sensors and had one in-clinic visit for venous blood reference tests. 40 out of the 120 participants wore additional Abbott Libre sensors and performed at least 7 capillary BG tests daily for additional reference and comparison. Continuous glucose error grid analysis (CG-EGA) showed that AiDEX and Abbott Libre had good agreement with venous blood glucose, with 98.69% and 98.96% accurate readings, respectively. Overall MARD of AiDEX CGM systems was 9.08% when compared to venous blood reference and 10.1% when compared to finger capillary BG reference.

Keywords

continuous glucose monitoring system, comparison study, factory calibration, flash glucose monitoring

Introduction

In this study, we conducted a clinical evaluation of the AiDEX CGMS (Microtech Medical (Hangzhou) Co. Ltd., Zhejiang, China) featuring real-time glucose monitoring and alerts and factory calibrated, 14 day-use glucose-oxidase-based electrochemical sensor.[1] Factory-calibration was achieved by producing sensor batches with low variability and factory calibration technologies including auto-coding and current/impedance sensing mode for automatic output adjustments.[2] The studied system consists of 3 components: a single-use glucose sensor pre-assembled into a sensor applicator which can be applied to skin through one simple action, a reusable transmitter, and a display unit with built-in glucose meter functions (Figure 1). The dimensions of the wearable parts of the CGMS including sensor and transmitter were 36 mm(L) * 22 mm(W) * 8 mm(H). The sensing range was 36 to 450 mg/dL and glucose readings can be sent to the receiver unit wirelessly via Bluetooth technology every 5 minutes so that the users have the benefit of real-time alerts.

Methods

A multicenter, prospective, single-arm, masked clinical study was conducted at 4 clinical sites. The protocol and informed

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Figure 1. Illustration of the studied CGMS devices. The system consists of a glucose-oxidase based electrochemical sensor attached to a reusable transmitter and a reusable data display unit, as well as a single-use sensor applicator to apply the sensor insertion site.

consent were approved by the internal review board and ethics committee of all participated sites in accordance with the Declaration of Helsinki. All subjects provided written informed consent before their enrollment.

A total of 120 eligible participants with age at least 14 years and are diagnosed with type 1 or type 2 diabetes were enrolled in this study with 30 enrollments at each of the 4 clinical sites. Each participant wore 4 studied sensors simultaneously on the back of left and right upper arm, left and right abdomen, respectively for up to 14 days. The participants were expected to maintain their usual daily activities and established diabetes regimen, including oral medication and/or insulin injection. Half of the total participants stay hospitalized throughout the sensor wearing duration and the rest wore sensors at their home environment.

The CGM and reference blood glucose readings as well as alerts were masked to the patients in order to prevent intentional self-manipulation of their own glucose level.

In addition, 40 out of the 60 hospitalized participants were randomly selected to simultaneously enroll in a comparison study and wore an additional Abbott Libre (Abbott Diabetes Care Ltd, Oxon, UK) sensor and were requested to perform at least 7 capillary BG tests daily on their own, using a Roche Accu-Check Performa BG meter (Roche Diagnostics Corporation, Indianapolis, IN, USA) during sensor wear period. The 7-point BG profile was intended reflect typical SMBG practice of patients with diabetes and were performed at 7:00, 9:00, 11:00, 13:30, 17:00, 19:00, and 21:00, respectively with a time window of ±30 min. The comparison between SMBG values and CGM readings provided information on how regular patient would perceive the accuracy of the studied CGMS.

Each participant was randomly scheduled and equally distributed to attend one in-clinic visits out of the 3 options: the second day after sensor insertion; between day 6 and day 8, and at day 14 after insertion, when venous blood samples were collected every 15 minutes over an 8-hour period for YSI analyzer reference tests. Participants were offered at least 1 meal and provided access to drinks and snacks during in-clinic visits. There was no intentional induction of hypoglycemia or hyperglycemia to the participants.

The studied devices report glucose readings every 5 minutes. Therefore, after each time a venous blood sample was taken for YSI reference test, the next updated CGM reading (ie, the new readings within 0 to 5 minutes after the collection of the venous blood sample) from the CGMS were recorded for comparison. For Libre sensors, a scan was performed immediately after the collection of venous blood sample and the scan readings were recorded for analysis.

At the end of the 14-day wearing time, the participants were requested to complete a post-study questionnaire describing their experiences. Key questions including pain rating during insertion and preference of real-time display of BG information or scanning for BG information.

Accuracy of the CGM system was evaluated by consensus error grid analysis,[3] Clarke error grid analysis,[4] continuous glucose error grid analysis (CG-EGA),[5] 15/15%, 20/20%, 30/30% agreement analysis, mean absolute relative difference (MARD) and regression statistics between the sensor glucose values and reference YSI venous blood glucose measurements. The lag between the CGM and YSI reference was evaluated by performing least square linear regression of the difference between the sensor glucose and YSI vs the sensor rate of change. Overall coefficient of variation is calculated by taking the average value of standard deviation divided by average values of the sensor glucose readings at 4 wear sites of each single data point. The high and low glucose alert threshold of the real-time CGMS were set to be 200 mg/dL and 80 mg/dL respectively, true alert (alerts that occur within ±30 min of a YSI measured high/low glucose event) and false alert (alerts that occur when no YSI measured high/low glucose event were found within ±30 min window) rates were calculated. Sensor survival rate per day as well as questionnaire responses and adverse events were also analyzed and summarized. Analyses were carried out using SAS version 9.2 software (SAS Institute, Cary, NC, USA).

Results and Discussion

A total of 480 AiDEX sensors were inserted to 120 participants. The baseline demographic characteristics of

Table 1a. Baseline Characteristics of Evaluable Study Participants ($n = 115$).

	Mean ± SD	Median	Range
Age (years)	60.2 ± 10.8	62	18-76
Height (cm)	165.1 ± 8.1	165	141-186
Weight (kg)	69.8 ± 12.4	68.9	40-110
BMI (kg/m^2)	25.5 ± 3.8	25.2	16.4-39.9
HbA1c (%)	7.42 ± 0.93	7.3	5.8-11.2
Years since diagnosis	12.5 ± 9.0	11.5	0.17-52

Table 1b. Demographic Characteristics of Evaluable Study Participants ($n = 115$).

Characteristics	Number of participants	%
Gender		
Male	57	49.6
Female	58	50.4
Diabetes type		
Type 1	14	11.3
Type 2	101	88.7
Medication		
Oral medicine	81	70.4
Insulin	57	49.6
None	8	7.0

the evaluable study participants as well as their diabetes management information were summarized in Table 1a and b, respectively. Among them 114 participants successfully completed the study with a total of 442 studied sensors and 36 Libre sensors returned valid data having paired reference blood glucose measurements. 1 participant withdrew from the study after the in-clinic session due to personal matter, and the data collected during the session were used in the accuracy analysis.

All valid data were used for analysis. A total of 3762 YSI reference glucose data ranging from 52 to 473 mg/dL were paired with 14586 sensor glucose data. In addition, 1188 of the YSI data from 36 comparison-study participants also had valid paired Abbott Libre data. Consensus and Clarke Error Grid Analysis (EGA) for AiDEX and Abbott Libre were shown in Figures 2 and 3, respectively. While both tested CGM systems had nearly 100% combined Zone A and B data points for consensus and Clarke EGA, the percentage of Zone A points for Abbott Libre were significantly lower (60.61% and 65.15% in consensus and Clarke EGA, respectively) and a large proportion of sensor glucose readings had a negative bias (Figure 3a and b). Given that the trending information of Libre FGM was still accurate, it demonstrated the benefits of CGM systems offering custom calibration function to improve accuracy performance.

A detailed CG-EGA accuracy analysis including sensor performances in hypoglycemic (blood glucose ≤70 mg/dL), euglycemic (70 mg/dL <blood glucose ≤180 mg/dL) and hyperglycemic ranges (blood glucose >180 mg/dL) for AiDEX and Abbott Libre were presented in Tables 2 and 3. The overall percentage of accurate readings of the 2 systems were similar at 98.69% and 98.96%, respectively. Both systems had a small percentage of erroneous readings (0.35% and 0.26%, respectively).

Results of 15/15%, 20/20%, 30/30% agreement analysis and the respective were shown in Figure 4 and Table 4. 95.8% of the total sensor readings were within ±20 mg/dL or ±20% of venous YSI reference values. The overall MARD for the studied CGM systems was 9.08%. The accuracy results were comparable to some of the current state-of-the-art factory calibrated CGMS products including Dexcom G6 (Dexcom Inc. San Diego, CA, USA) and Abbott Libre, with reported MARD of 9.0% and 9.4%, respectively.[6,7,8,9]

There were no significant differences between sensor accuracy at different wear locations, with an overall coefficient of variation (CV) of only 3.98%. Allowing insertion on both upper arm and abdomen without the need to worry about performance difference is beneficiary to patients who might have a site preference or need to rotate between different insertion sites.

Regression analysis showed high agreement between the sensor glucose results compared to venous YSI readings, with slope of 0.89, intercept of 0.63 mmol/L, and correlation coefficient of 0.959. The mean lag time between the sensor and YSI reference was 4.59 minutes, with a 95% confidence interval of 4.17 to 5.01 minutes.

The accuracy of the real-time alerts was summarized in Table 5. Both low and high glucose alerts have a true alert ratio above 90%, and less than 1% of the alerts were false.

In addition, 3643 fingertip capillary BG measurements were collected from 38 non-withdrawal subjects. The CGM system had an overall MARD of 10.1%, and 92.4% of the total sensor readings were within ±20 mg/dL or ±20% of capillary BG reference values. The slope of sensor glucose readings vs. capillary BG readings were 0.91 with intercept at 0.45, the calculated correlation coefficients was 0.93. For the first day, the capillary BG MARD was 11.7% ($n = 195$), higher than the rest of the days (For Day 2-14, overall MARD = 10.0%, $n = 3448$).

Sensor survival rate vs wearing days were summarized in Figure 5. By the end of the study, 22 (4.74%) sensors were dislodged or fell off before the intended 14-day wear ends. 18 (7.9%) were inserted on the back of the upper arms and 4 (1.8%) were on the abdomen. Response from the participants indicated that the majority of the dislodgement were caused by hitting the devices at wall corners or door frames, or stuck clothes or towels between the sensor and the base patch.

15 adverse events were reported by 8 of the 120 participants. Anticipated adverse events included bleeding and

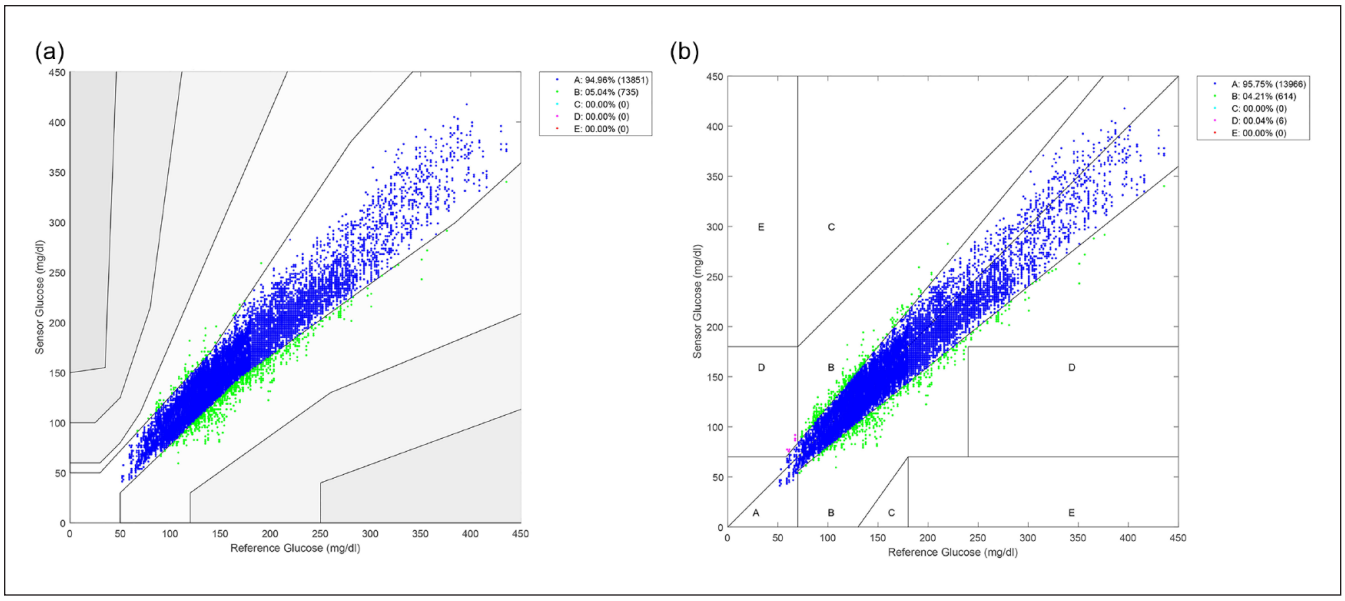

Figure 2. Accuracy analysis for AiDEX real-time CGM readings vs YSI reference values. (a) Consensus error grid analysis chart. (b) Clarke error grid analysis chart.

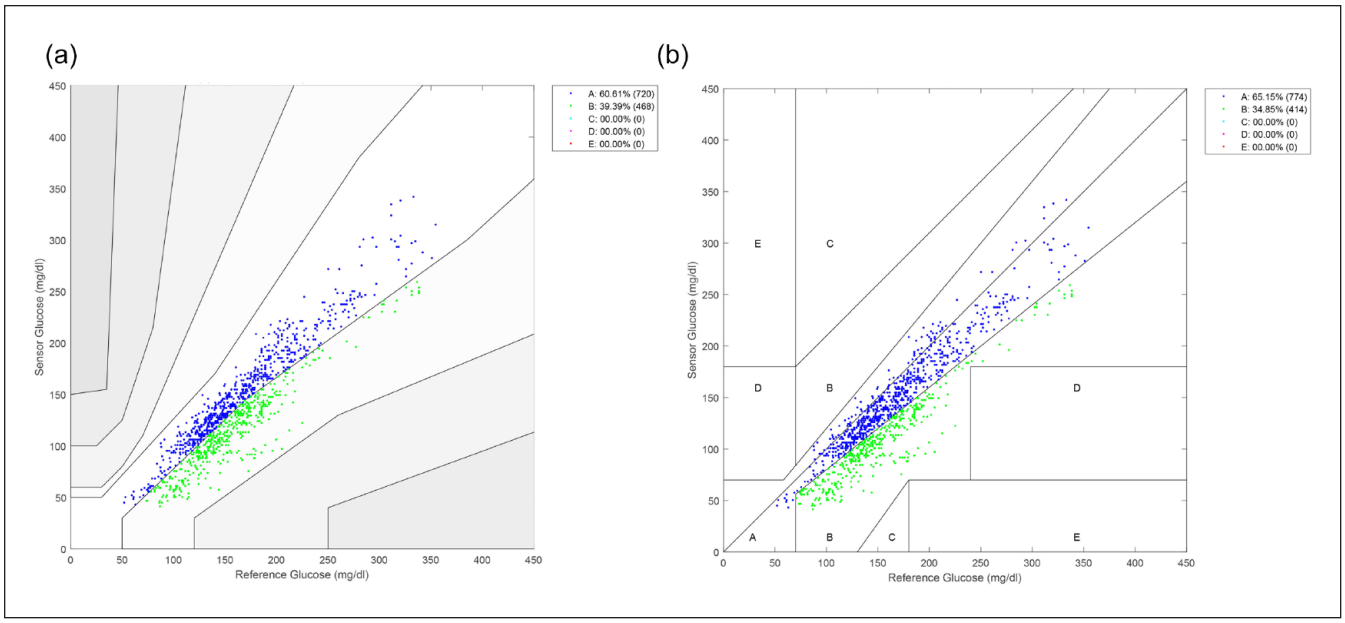

Figure 3. Accuracy analysis for Abbott Libre FGM readings vs YSI reference values. (a) Consensus error grid analysis chart. (b) Clarke error grid analysis chart.

Table 2a. Continuous Glucose Error Grid Analysis for AiDEX CGM System.

	Hypoglycemia BG ≤ 70 mg/dl		Euglycemia 70 < BG ≤ 180 mg/dl		Hyperglycemia BG > 180 mg/dl		Overall	
CG-EGA	%	*n*	%	*n*	%	*n*	%	*n*
Accurate	93.48	86	98.94	9233	98.31	4640	98.69	13959
Benign	0.00	0	0.95	89	1.00	47	0.96	136
Erroneous	6.52	6	0.11	10	0.70	33	0.35	49

Table 2b. AiDEX CGM Accuracy Analysis vs. YSI Reference.

	Hypoglycemia BG ≤ 70 mg/dl		Euglycemia 70 < BG ≤ 180 mg/dl		Hyperglycemia BG > 180 mg/dl		Overall	
Wear duration	MAD(mg/dl)	*n*	MARD(%)	*n*	MARD(%)	*n*	MARD(%)	*n*
Day 2	8.40	24	9.77	3180	9.11	2043	9.53	5247
Day 6-8	6.60	35	8.47	3430	7.66	1320	8.26	4785
Day 14	11.17	33	9.48	2974	9.14	1547	9.42	4554
Overall	8.71	92	9.22	9584	8.73	4910	9.08	14586

Table 3a. Continuous Glucose Error Grid Analysis for Abbott Libre FGM system.

	Hypoglycemia BG ≤70 mg/dl		Euglycemia 70 <BG≤ 180 mg/dl		Hyperglycemia BG >180 mg/dl		Overall	
CG-EGA	%	*n*	%	*n*	%	*n*	%	*n*
Accurate	100	9	99.88	809	96.70	322	98.96	1140
Benign	0.00	0	0.12	1	2.40	8	0.78	9
Erroneous	0.00	0	0.00	0	0.90	3	0.26	3

Table 3b. Abbott Libre FGM Accuracy Analysis vs. YSI Reference.

	Hypoglycemia BG ≤ 70 mg/dl		Euglycemia 70 < BG ≤ 180 mg/dl		Hyperglycemia BG > 180 mg/dl		Overall	
Wear duration	MAD(mg/dl)	*n*	MARD(%)	*n*	MARD(%)	*n*	MARD(%)	*n*
Day 2	19.62	1	16.49	277	13.69	151	15.54	429
Day 6-8	9.68	5	13.27	248	9.86	110	12.28	363
Day 14	8.34	3	23.99	309	20.82	84	23.24	396
Overall	10.34	9	18.31	834	14.20	345	17.11	1188

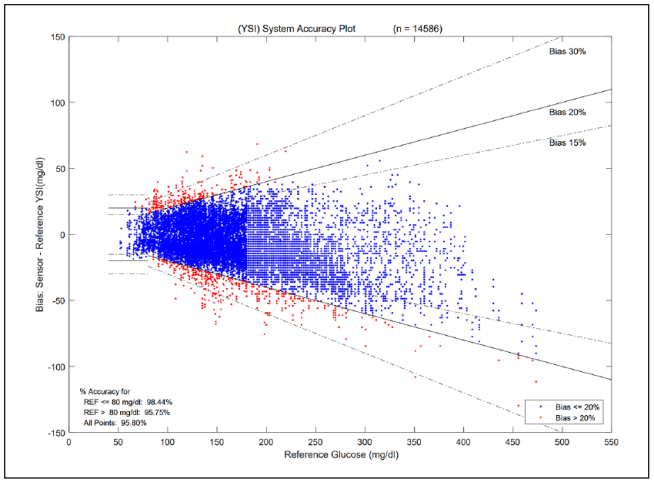

Figure 4. 15/15%, 20/20%, and 30/30% sensor agreement analysis of the AIDEX CGM system vs YSI reference glucose values.

pain during insertion, erythema, itchiness or skin irritation at sensor adhesive patch application sites, all of these were commonly observed in other CGM systems.[10,11]

The ease-of-use measures of the system were reflected by the participants' responses to the post-study questionnaires. Most participants rated the devices to have no or minimal pain during insertion (92.2%), and almost all participants preferred real-time glucose reading display concept over the Flash Glucose monitoring system.

Conclusions

In this prospective, multicenter study, a 14-day use factory-calibrated real-time continuous glucose monitoring system was evaluated in diabetic populations. The performance of the system was established by its accuracy across all clinically relevant glucose ranges with respect to reference measurement.

Table 4. 15/15%, 20/20%, and 30/30% Sensor Agreement Analysis Showing Point Estimation With Lower Boundaries of 95% Confidence Intervals.

BG ≤80 mg/dl		BG ≥ 80 mg/dl		Overall	
N	320 (%)	*n* (%)	14266 (%)	*n* (%)	14586 (%)
bias ≤ 15 mg/dL	92.19 (86.71)	bias ≤ 15	86.28 (85.46)	bias ≤ 15/15	86.40 (85.59)
bias ≤ 20 mg/dL	98.44 (92.96)	bias ≤ 20	95.75 (94.93)	bias ≤ 20/20	95.80 (94.99)
bias ≤ 30 mg/dL	100.00 (94.52)	bias ≤ 30	99.50 (98.68)	bias ≤ 30/30	99.51 (98.70)

Table 5. Alert Accuracy Analysis.

YSI readings		Number and percentage of alerts	
<70 mg/dL	79	True low alerts	76 (96.2%)
>200 mg/dL	917	True high alerts	829 (90.4%)
70-200 mg/dL	2766	False low alerts	10 (0.27%)
		False high alerts	20 (0.70%)

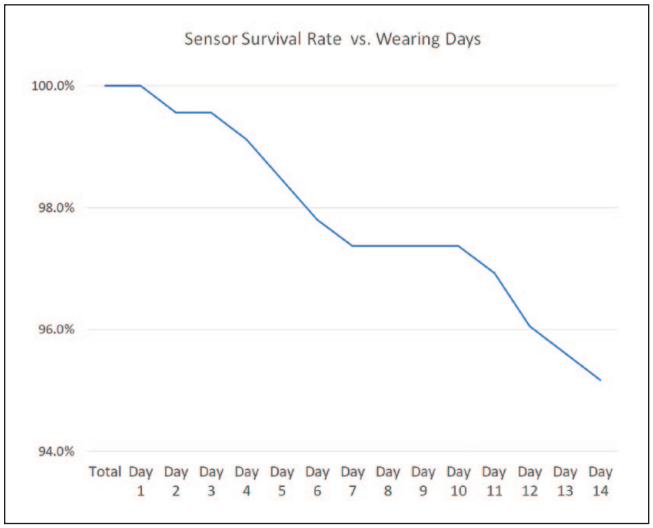

Figure 5. Sensor survival rate with respect to wearing days.

Abbreviations

CG-EGA, continuous glucose error grid analysis; CGM, continuous glucose monitoring; FGM, flash glucose monitoring; MARD, mean absolute relative difference; SMBG, self-monitored blood glucose; YSI, yellow spring instruments.

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Author Contributions

J.L., L.G., J.Z. and Y.L. designed the study and were responsible for data collection, interpretation of data, and analysis. Z.C. was responsible for statistical analysis. Including MARD and Clarke error grid data analysis. All authors contributed to the feedback and revisions for the final article.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Z.C. is currently an employee of Microtech Medical (Hangzhou) Co. Ltd. No other potential conflicts of interest relevant to this article were reported.

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