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Research Article

Data Analysis and Accuracy Evaluation of a Continuous Glucose-Monitoring Device

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This study was aimed at analyzing data and evaluating the accuracy of a new subcutaneous continuous glucose-monitoring device by referring to finger-pricking measurement. The data were obtained from 7 diabetic patients. An improved implanted flex sensor was used to measure the interstitial glucose concentration every 3 min within 6 days, and five finger-pricking samples were collected every day for comparison. A periodic glucose change happened every day. 2.45% of CGM values were in the hypoglycemic range (<70 mg/dl), 55.4% were in the normal range (70-180 mg/dl), and 42.15% were in the hyperglycemic range (>180 mg/dl). The interstitial glucose concentrations ($n = 204$) were well linearly correlated with the capillary glucose concentrations ($r = 0.94$, $P < 0.01$), but a delay occurred between 10 and 40 minutes within two measurements (CGM later), and the individual average delay times were relatively close to 24.6 minutes. Clarke's error grid analysis showed that 86.7% of the points fell in zone A, 12.7% fell in zone B, and only 0.6% fell in zone D. An overall MARD was 10.22%. This study demonstrated that the CGM was accurate and highly reliable; thus, it constituted a new device for continuous glucose monitoring in diabetic patients.

1. Introduction

The World Health Organization (WHO) published the Global Report on Diabetes 2016 [1], which showed that global adult diabetes increased three times in the recent 40 years, and most of them lived in developing countries. The population of global diabetics above the age of 18 was 108 million before the 1980s, but it increased to 422 million in 2014, accounting for 8.5% of the world's population. In 2012, diabetes directly led to the deaths of 1.5 million people. In addition, cardiovascular and other diseases associated with hyperglycemia death account for 2.2 million. Therefore, the WHO forecasted that by 2030, diabetes will become the seventh largest cause of deaths. The report indicated that it was difficult to substantially reduce the number of diabetes proportion, and the patients would rise more rapidly in low- and middle-income countries. Most diabetics lived in the Western Pacific area and were estimated to be 131 million, while the second region (around 96 million) was in Southeast Asia. Among them, Chinese diabetics were over 70 million, and it had become the leading diabetes country [2, 3].

The glucose in the blood bears the responsibility for each organization cell of the human body to provide the required energy, so the glucose levels must be maintained in a stable range to guarantee the need of the human body. However, the high glucose concentration in diabetics could lead to serious complications including kidney failure, stroke, heart attack, high blood pressure, blindness, and coma [4]. Therefore, strict metabolic control is greatly helpful to control the occurrence and worsening of microvascular complications of both type II diabetes (T2D) and type I diabetes (T1D) [5]. In recent years, the technologies for self-monitoring of glucose levels have been greatly developed, and people can achieve good metabolic control by themselves. The glucose level should be detected at least twice or four times a day with finger-pricking for T2D patients or T1D patients, respectively [6–8]. Finger-pricking can only offer the information

Table 1: Summarize of the patients' characteristics.

Parameter	Value
Number of patients	7
Duration (days)	6
Age (years)	42 (24-55)
Sex (male/female)	4/3
Duration of diabetes (years)	16 (5-31)
BMI (kg/m^2)	25.5 (20.5-33.1)
Systolic blood pressure (mmHg)	123 (101-140)
Diastolic blood pressure (mmHg)	77 (70-89)

like a cascade of photos, and they are often missing glucose fluctuations during the whole day. As a result, continuous glucose monitoring (CGM) is considered the best way to provide the continuous information, just like a movie that is showing. Recently, minimally invasive techniques have been proposed for CGM to better monitor subcutaneous glucose concentration, which refers to the concentration in the subcutaneous adipose tissue fluid [9, 10]. It has been identified that the interstitial glucose (IG) concentration is closed to the glucose concentration in capillaries in many cases [11, 12]. By providing automatic and frequent determinations of the IG level, the CGM would monitor the glycemic fluctuations and thus identify glucose trends in diabetic patients without frequent finger-pricking tests.

Currently, CGM products approved by FDA on the market are mainly derived from Medtronic, Dexcom, and Abbott [12]. Among them, the CGM from Medtronic is the only approved device by the Chinese government. The device is mainly composed of two components: a flat film platinum sensor and a data recorder. The device is mainly used to monitor patients within 72 hours and is mostly used in the ICU of hospitals.

The purpose of this work is to introduce an improved type of CGM device, analyze the information in the data, and evaluate the accuracy and efficacy of the data in both T2D patients and T1D patients. The current device includes an improved four-electrode implanted sensor with a longer life expectancy, a recorder, and a wireless receiver. The recorder takes a glucose measurement every second through the implanted sensor and sends an average value every three minutes to the wireless receiver. Then, the current value and glycemic curve are shown on the receiver. Such a device can offer an individual continuous glucose monitoring up to 6 days.

2. Experimental

2.1. Diabetic Patients. There were 7 diabetic patients (3 women and 4 men) who were selected from a local hospital participating in this study. The patients' characteristics are shown in Table 1, and some of these values were expressed as the mean value. For example, the mean age was 42 years, ranging from 24 to 55 years. In addition, the mean duration for diabetes of such patients was 16 years since the first diagnosis, and the mean Body Mass Index (BMI) was 25.5 kg/m^2. Beyond those, the mean systolic blood pressure of patients was 123 mmHg, and the mean diastolic blood pressure was 77 mmHg. The study (6 days) was a nonrandomized trial conducted under free-living conditions (e.g., exercise and diet), and at same time, all patients took the medicine (e.g., insulin, metformin) as usual.

2.2. Devices. An improved CGM device is introduced in this study, as shown in Figure 1, which is the POCTech CT-100 from Zhejiang POCTech Co. Ltd., China. All participants would wear the CGM devices before the test begins without any discomfort. The device includes three components: a flex sensor, a recorder, and a wireless receiver. Among them, the improved flex sensor, currently implanted comfortably into the subcutaneous tissue layer (approximately 2 and 3 cm to the left or right lateral aspect of the umbilicus) by a special device as shown in Figure 1, has a three-dimensional four-electrode structure. There is an implantation diagram of the flex sensor in Figure 2. In the three-dimensional structure, a blank electrode (BE) is added to the three-electrode (working electrode (WE), reference electrode (RE), and counter electrode (CE)) system, and the 3D structure is shown Figure 3. Each electrode is printed on a flexible substrate and then superimposed to form a flexible sensor; at last, the flexibility of the sensor increases the comfort of wearing. In addition, an interference current I_{BE} ($I_{BE} = I_I$) is measured by the BE, and a mixed signal (I_{WE}) is measured by the WE which includes the I_G and I_I, so it would help to remove the interference and obtain a purer glucose signal for measuring the interstitial glucose (IG) concentration with better sensitivity and accuracy. The sensor insertion site also could be placed in the abdomen or the upper arm without local anesthesia, just so it is not affected by daily activities [13, 14]. On the other hand, the recorder is separated from the sensor with a small size and waterproof and easy to be carried. Therefore, this design is convenient for replacing recorder batteries or sensors to reduce the cost of consumables.

The sensor contains glucose oxidase and oxidized glucose to gluconolactone while reducing oxygen to hydrogen peroxide. When the produced peroxide reacts with platinum inside the sensor, it generates electrical signals. At this time, the recorder converts the electrical signal into a glucose reading by a special program and then sends the reading to the wireless receiver to store and display. As can be seen from Figure 3, the improved three-dimensional structure of the sensor would contain more glucose oxidases between layers to give a life span of more than six days.

Finger-pricking is the capillary glucose measurement derived from the conventional glucose meter served as the reference standard. The glucometer device is the Roche CR2032 from Roche Diabetes Care, Inc., Indianapolis, USA. All participants are provided one-off test strips and lancets.

2.3. Measurement. A small bioflexible sensor was inserted subcutaneously in the abdomen region or upper arms for the interstitial glucose sampling in a 6-day period, and during that time, five finger blood samples were collected every day.

In order to ensure the consistency of the experiment, every patient was required to wear the CGM on the

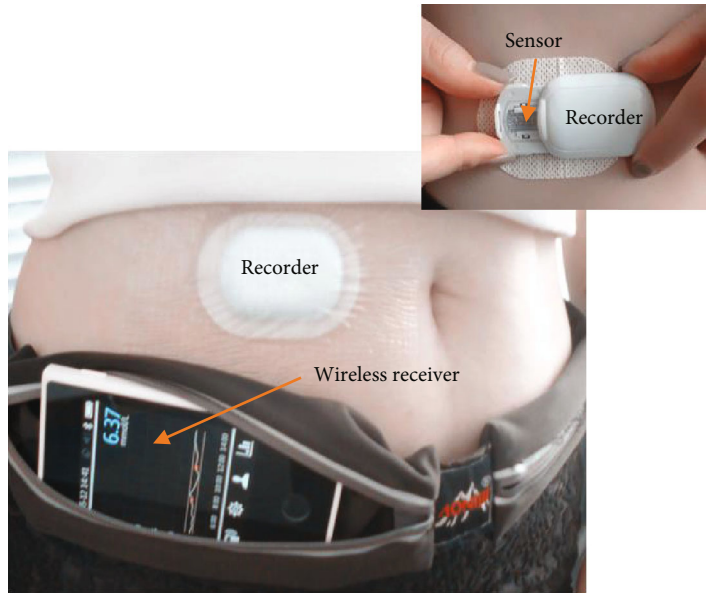

Figure 1: Wearing diagram of a continuous glucose-monitoring device.

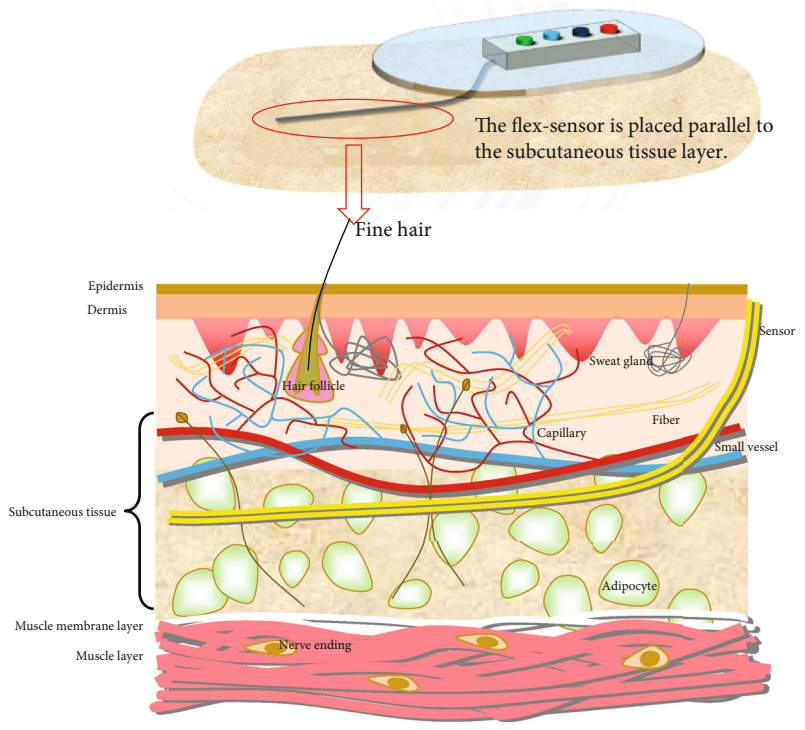

Figure 2: Implantation diagram of a flex sensor.

abdomen. Before the sensor insertion, this sensor was removed from the freezer and would take at least 30 minutes to return to room temperature. The start time of wearing the sensor should be selected just after breakfast or lunch, so as to ensure completion of the three-hour initialization. After the initialization, a finger blood glucose (BG) was measured by a glucometer in the period of blood glucose stabilization, which was between greater than 2 hours after the meal and before the next meal, and the BG was input to the receiver for the first calibration within 3 minutes. The receiver then began to display a continuous glucose curve. The second blood sampling calibration would have been done in 6-10 hours before dinner or bedtime. In addition, a finger blood sampling calibration before breakfast every day and

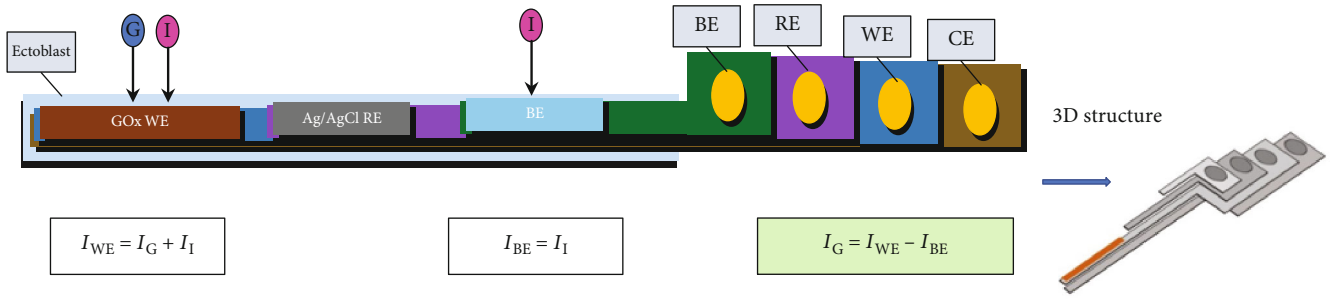

Figure 3: Internal structure drawing of the flexible sensor.

one before dinner of the second day were done to ensure the validity of continuous glucose data. All the operations were described on the manufacturer's website [15]. An IG was detected once per second by the CGM, and a mean IG of three minutes was continuously sent to the receiver during the six days. So, eventually, there were about 2,880 data (480 data per 24 h period) stored. Five blood glucose concentrations were collected during the 24 h period at the following times: 6:00 A.M. before breakfast, 2 h before lunch, 1 h after lunch, before dinner, and 2 h after dinner. Finally, a total of 204 effective blood glucose data (about 29 per person) was collected from seven people.

2.4. Statistical Analysis. Statistical analyses were performed using Microsoft Excel 2016 (Microsoft Corp., Redmond, WA, USA), MATLAB R2014a (The MathWorks, Inc., Natick, MA, USA), and Origin 8.6 (OriginLab Corp., Hampton, MA, USA). By the least square method, linear regression analysis of IG and BG data was carried out. Statistical evaluation of the slopes of the regression lines was performed by the F distribution test. Since the BG value was earlier than the IG, the time delay was a time difference between the closed BG value and the IG value. Using the statistical method, when the number of big error data of IG and BG exceeded 1% ($P > 0.01$), it indicates that there was a significant difference between IG and BG. The Clarke error grid analysis was used to evaluate the clinical consistency/-discrepancy between IG and BG measurements. A mean absolute relative difference (MARD) between IG and BG was shown in glucose physiological tolerance. The percentage bias is shown in a box chart.

3. Result Analysis

Figure 4 shows two CGM curves for 6 days, and they are typical profiles obtained with this measuring scheme from seven patients. In each graph, the blue line represented the IG concentration and red dots as the references represented the capillary blood glucose concentration. The nonlinear characteristic of blood glucose change could be seen from the blue curve. Therefore, the possibility of linear derivation of the glucose value was excluded. It was found by calculation that 5.36% (bias > 30%) of the reference points (red dots) deviated largely from the IG value in the 204 data. What is more, there was a lag time between the interstitial glucose concentration and the capillary glucose concentration. It showed the delay time distribution at various reference concentrations in Figure 5(a), and the average delay of each patient is shown in Figure 5(b) [16]. As can be seen from the above diagrams, the delay was caused by multiple factors and it was not a stable value in a relatively large range (maximum > 60 minutes). The delay was mainly distributed between 10 and 40 minutes, and the average delay times of the seven persons were around 24.6 minutes. This delay would have some effect on daily treatment, especially in the use of insulin pump therapy.

One patient was selected, and a 24 h monitoring curve for 6 consecutive days is shown in Figure 6. It gave us clear information that the glucose value changed in a certain periodic time: although the glucose level fluctuated after meals, the rise and decline times of glucose after meals were started at the same periodic time. For instance, after breakfast, glucose levels fluctuated differently, but the duration of rising and declining of glucose started and ended, respectively, at 7:25-9:50 A.M. and 9:50-11:15 A.M. Moreover, after meals, the glucose level dropped faster during the daytime than the night. The lowest point of the daytime usually occurred at about 5:30 P.M. or before dinner, but the lowest point of the night with reference to the glucose value of finger-pricking usually occurred at about 5:00 A.M. or before breakfast. Beyond those, the glucose level almost began to decline two hours after every meal (after 10:00 A.M., 1:30 P.M., and 8:00 P.M.). From the above analysis, we know that the CGM data help not only to obtain the blood glucose level but also to find rules of continuous change of blood glucose, such as the occurrence time of hypoglycemia.

The hypoglycemic range is below 70 mg/dl, and the hyperglycemic range is above 180 mg/dl. We compare the glucose values of the finger-pricking and CGM. Analysis of the capillary glucose results showed that 2.45% of data were in the hypoglycemic range, 55.4% of the testing were sitting in the normal range, while 42.15% were in the hyperglycemic range. As shown in Figure 7, the interstitial glucose concentrations in this group of patients were well linearly correlated with the blood glucose concentrations. The regression coefficient (r) was 0.94, the slope and slope standard error were, respectively, 0.9714 and 2.463%. The intercept and intercept standard error were, respectively, 3.995 mg/dl and 3.7454%.

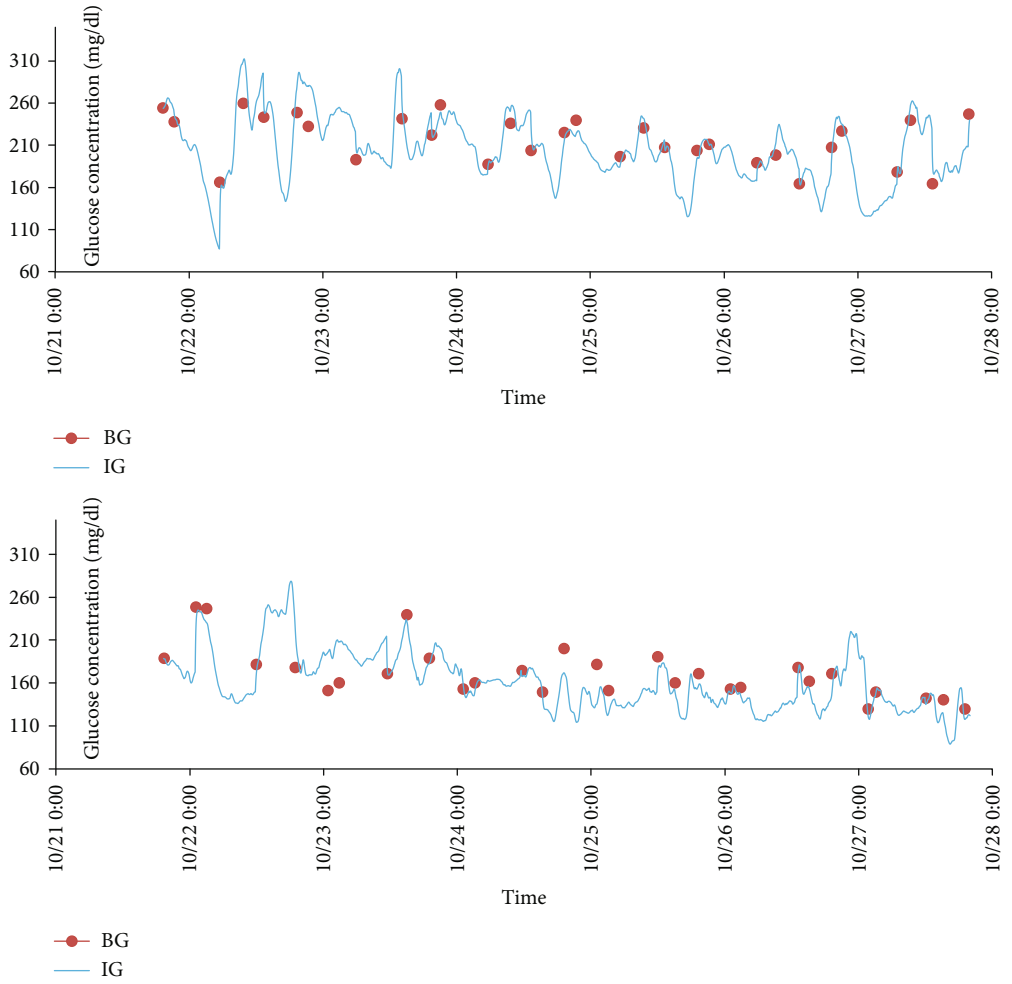

Figure 4: Two typical CGM curves for 6 days.

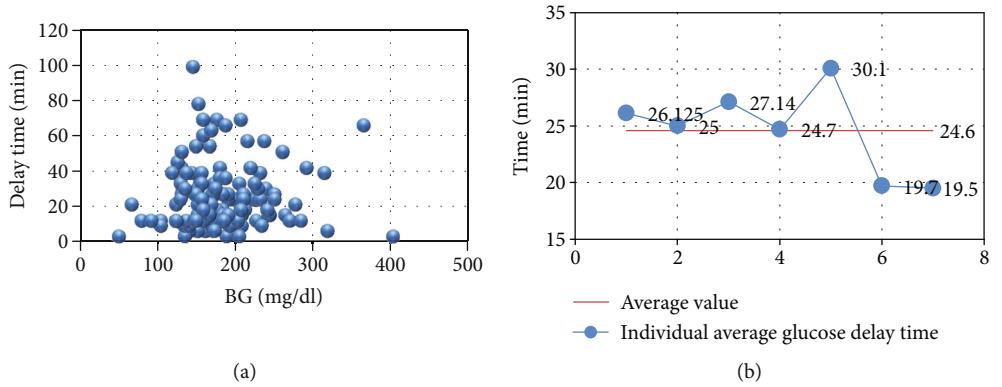

Figure 5: Delay time distribution at various reference concentrations in diagram (a); average delay of each patient was shown in diagram (b).

In the glucose physiological range, there was no significant difference between IG and BG ($P < 0.01$).

The Clarke error grid analysis was used to evaluate the clinical consistency/discrepancy between IG and BG measurements in Figure 7 [17]. The IG values monitored by the CGM with a Cartesian diagram were displayed on the y-axis, and the BG values were demonstrated on the x-axis. The diagonal represented a good consistency between the two values, while points below and above the diagonal indicate overestimation or underestimation of the reference values, respectively. The glucose values, which deviated by <20% from the reference values, belonged to the zone

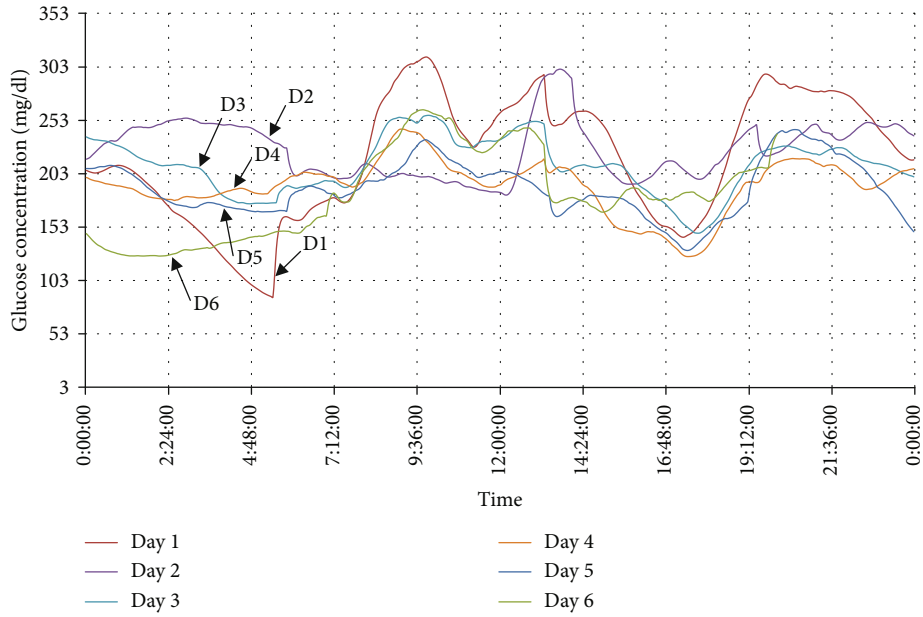

Figure 6: The glucose level profile for 24 h within consecutive 6 days. D1-D6 represent day 1-day 6, respectively.

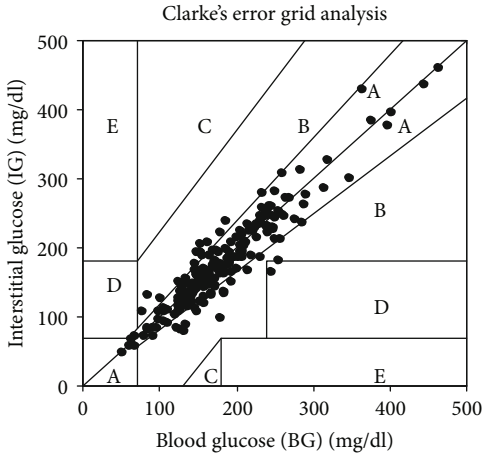

Figure 7: Linear regression analysis and Clarke's error grid analysis for all values in one patient ($n = 204$, $r = 0.94$, $r^2 = 0.8845$, $P < 0.01$, slope = 0.9714 mg/dl).

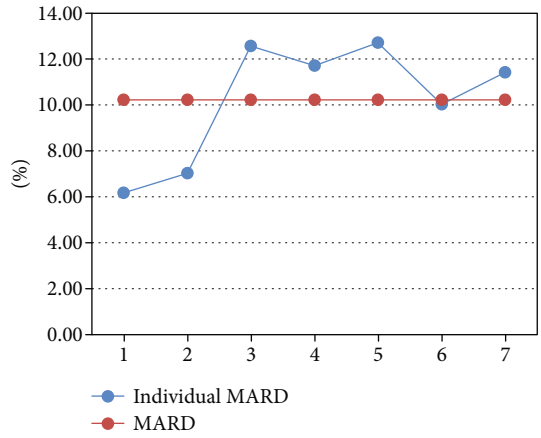

Figure 8: MARD distribution diagram.

A. In addition, the zone A also included the IG values in the hypoglycemic range, whereas the BG values were also within the hypoglycemic range. The values in this zone A were clinically accurate and normally used as a basis for clinical diagnosis. The glucose values, which deviated by >20% from the reference values, belong to the zone B, which was above and below zone A. The values in zone B were benign errors and thus can be classified as acceptable clinical data. As a result, the points that fell in zones A and B were clinically acceptable, whereas the points that fell in zones C–E represented too big a deviation to accept, and the values in zones C–E would give rise to some clinically significant mistakes. Clarke's error grid analysis showed that 86.7% of the points fell in zone A, 12.7% in zone B, and only 0.6% in the unacceptable zone D, while no points were detected in zones C and E. In the end, the Clark grid error analysis results show that the data from CGM are clinically acceptable data.

In this paper, MARD was used to evaluate the difference between BG and IG, and the MARD of each patient and the overall MARD are shown in Figure 8. The MARD results showed that there were differences among individuals, and the overall MARD of 10.22% showed that the IG result was acceptable. As shown in a box chart of the percentage bias between IG and BG in Figure 9, the bias is 8.26% in the hypoglycemic range (<70 mg/dl), 11.92% in the euglycemic range (70–180 mg/dl), and 8.11% in the hyperglycemic range (>180 mg/dl).

4. Discussion

Continuous glucose monitoring is a better self-monitoring way of blood glucose for both type 1 and type 2 diabetic

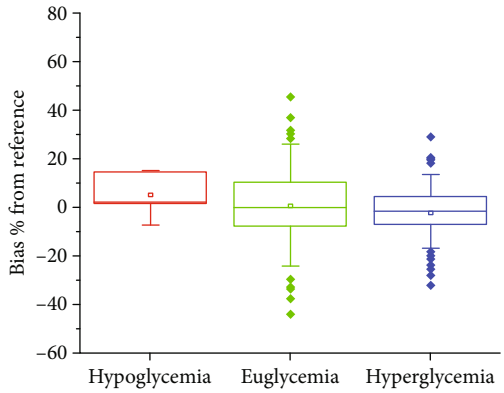

Figure 9: Box chart of the percentage bias between IG and BG.

patients. Compared to the previous finger-pricking measurement, this CGM system can monitor the individual glucose daily fluctuation, trend, and occurrences of both hyperglycemia and hypoglycemia and is especially useful for monitoring hypoglycemia during the night. Moreover, the main complaint of the finger-pricking is the inconvenience and discomfort, as well as the high cost of testing strips. Beyond that, the number of finger-pricking is limited per day, so more comprehensive data are urgently needed from the continuous glucose monitoring.

The system in this study is easy for installing and changing the recorder battery and supports continuous testing for six days. The improved flex sensor is not only more convenient and comfortable for patients but also more stable for monitoring. In this study, it analyzed data and evaluated accuracy of an improved CGM used in continuous subcutaneous glucose monitoring. This system recorded the subcutaneous interstitial glucose concentration every 3 min; therefore, it obtained 480 samplings after a 24 h monitoring. Finger-pricking was taken five times a day, and CGM data of all patients were collected for 6 days; the following conclusion can be addressed after careful analysis: Firstly, as a result of regular life, the glucose value changed in a certain periodic time in the 24 h monitoring curve. The rise and decline times of glucose after meals started at the same periodic time. Therefore, a regular life can be adjusted to stabilize blood glucose levels. In the meantime, if we pay close attention to the duration of hypoglycemia and hyperglycemia, it can be found that 42.15% of values were in the hyperglycemic range, so treatments for patients needed to be strengthened especially after meals. Secondly, the study showed the delay time distribution at various reference concentrations. The delay was mainly located between 10 and 40 minutes. The instability of the delay time was related to the individual metabolism. The seven-person average delay times were relatively close to 24.6 minutes. Thirdly, only 5.36% of the interstitial glucose concentrations deviated largely (bias > 30%) from the reference points (BG) within the seven patients, and the regression coefficient (r) was 0.94. The interstitial glucose concentrations were well linearly correlated ($P < 0.01$) with the capillary glucose concentrations, and it showed that the accuracy of clinical monitoring has been basically achieved. Fourthly, as a result of the Clarke error grid analysis, the points that fell within clinically acceptable zones were 99.4%. An overall MARD from the reference (BG) was 10.22%, of which the regional percentage bias was 8.26% (hypoglycemic range), 11.92% (euglycemic range), and 8.11% (hyperglycemic range). Finally, its findings demonstrated that the CGM was accurate compared with the finger-pricking as the reference and could collect various parameters of continuous blood glucose to adjust their clinic treatment plan.

5. Conclusions

According to linear regression analysis and Clarke's error grid analysis in Figure 7, the improved CGM in this study can accurately monitor the glucose level in the clinic and also gives enough data to observe the changes of blood glucose. In addition, although the percentage deviation analysis in Figure 8 shows that IG has 10.22% MARD compared with BG, 5.36% of IG (bias > 30%) are still abnormal values. Therefore, the CGM needs further optimization. According to delay analysis in Figure 5, it tells us that before analyzing the CGM data, attention should be paid to the timeliness of data according to the differences of physical indicators and the metabolism speed in a day. Of course, all the data analyses still prove that the CGM is accurate. This CGM provides a new device for continuous glucose monitoring. Then, due to the limited test group and quantity in this study, the data may have some limitations. So, in the later stage, expanding the test group, increasing the number of test people, and upgrading the system hardware and software will be done to optimize the CGM.

Data Availability

Informed consent for data sharing was not obtained but the presented data are anonymized and risk of identification is low.

Conflicts of Interest

The first author received his B.S. degree from Suzhou University of Science and Technology, China, in 2009 and his M.S. degrees from Shanghai Maritime University, China, in 2011. Since 2011, he was an engineer at Shanghai Polytechnic University, China. Since 2015, he has been a PhD student at Tongji University, China. His research interests are in intelligent sensing and wireless network (ljcai@sspu.edu.cn). The second author received his B.S. and M.S. degrees from Harbin Institute of Technology, China, in 1982 and 1985, respectively, and his PhD degree from the University of Siegen, Germany, in 1998. From 1985 to 1992, he was an assistant professor at Huazhong University of Science and Technology, China. From 1992 to 1998, he was an assistant professor at the University of Siegen, Germany. Since 1998, he has been a professor at Tongji University, China. His research interests are in information and communication engineering (gwc828@tongji.edu.cn). The third author received a PhD degree from the Shanghai Institute of Ceramics, Chinese Academy of Sciences (2005),

where he worked on functional materials and devices. In 2009-2012, he was a research associate at the University of Cambridge working in MEMS design and fabrication for biosensors. Since March 2012, he is a Jinqiao professor at Shanghai Polytechnic University. He has published over 50 peer-reviewed journal papers so far, and his main research interests are micro-/nanobiosensors and chemical gas sensors (zgzhu@sspu.edu.cn). The fourth author received her B.S. degree from Xinyang Normal University, China, in 2009 and her PhD degrees from the East China University of Science and Technology, China, in 2014. From 2014 to present, she is a lecturer at Shanghai Polytechnic University. Her research interests focus on the development and application of nanomaterials, biosensors, nanozymes (xlzhao@sspu.edu.cn). The fifth author received his B.S. degree from Xiamen University, China, in 2009 and his PhD degrees from Xiamen University, China, and Université de Perpignan Via Domitia, France, in 2014 and 2015, respectively, under the cosupervision of Prof. Shi-Gang Sun and Prof. Jean-Louis Marty. Since 2015, he is an assistant professor at Shanghai Polytechnic University, China. His research interests are in electrochemical sensors, biosensors, and wearable devices (zhli@sspu.edu.cn). The authors declare that there is no conflict of interest regarding the publication of this paper.

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