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EDITORIAL

Continuous glucose monitoring in China: Then, now and in the future

Glucose monitoring is a key component in assessing glucose metabolic disturbance, evaluating therapeutic outcomes and guiding treatment regimens. As blood glucose fluctuates from time to time, self-monitoring of blood glucose fails to accurately reflect the blood glucose profile, because it only represents the glucose concentration at a specific time-point. Therefore, for decades, continuous glucose monitoring (CGM) was one of the dreams of patients with diabetes and diabetologists, as is still the case with closed-loop systems. The first-generation CGM system (CGMS) was approved in 1999. This monitoring system was a Holter-style monitor for clinical use only. However, the introduction of CGMS did not immediately revolutionize the treatment of diabetes. Since then, the performance of the glucose sensors and the algorithms used to analyze the data have improved substantially over the past decade, so that current CGMS outperforms the first generation system.

CGMS records continuous, comprehensive and reliable glucose levels using a subcutaneous sensor to monitor interstitial glucose levels. The CGM data provide 24-h tracking of blood glucose. This is in contrast to the single time-point data provided by self-monitoring blood glucose testing. The CGM indications include the following: increased risk for hypoglycemia, potential silent hypoglycemic episodes, lack of hypoglycemia awareness and elevation of postprandial glucose values. In China, the initial research on retrospective CGMS data was carried out in 2002. In 2007, the 'Chinese Continuous Glucose Monitoring Study Group' was formed by multiple centers across the nation. The group has established reference values for CGM parameters (Table 1).[1] The Chinese Diabetes Society then published the *Clinical Applications of Dynamic Blood Glucose Monitoring in China (2009 version)* in December 2009. After that, the Chinese Diabetes Society Glucose Monitoring Group was formed in 2010, and the committee updated the *Chinese clinical guideline for continuous glucose monitoring (2012)*.[2] These guidelines have substantially improved the application of CGM, and have increased comprehensive glucose management in China.

There are two principal types of CGMS devices, retrospective CGMS and real-time CGMS. The retrospective CGMS provides data for 3–5 days, depending on the duration of use. The system records readings every 5 min, which leads to approximately 288 daily readings. The retrospective system provides detailed information regarding the magnitude, duration and frequency of fluctuations. The system also provides information on glycemic excursions and glycemic variability. Using retrospective CGMS data, we identified the postprandial glucose excursion after breakfast was higher than that after lunch and dinner in Chinese patients. This finding might be attributed to hormones influencing glucose metabolism and to Eastern eating habits. Additionally, we have cooperated with several study centers and carried out a few studies to evaluate therapeutic outcomes by CGMS (Table 2). A randomized, active-comparator trial was carried out in 40 newly diagnosed type 2 diabetes patients whose glycated hemoglobin ranged from 7 to 9.8%. The participants were randomized (1:1 ratio) to receive a glipizide controlled-release tablet alone (5 mg) or glipizide in combination with acarbose 50 mg b.i.d. for 8 weeks. The study results showed that both regimens improved glycated hemoglobin levels, the mean amplitude of glycemic excursion (MAGE) and the intraday glycemic variability parameter. The data showed that the combination therapy was more effective in reducing intraday and day-to-day glycemic variability than was glipizide monotherapy.[3] We subsequently carried out a multicenter, open-label, randomized, active-controlled, parallel-group study to compare the therapeutic effect on improving postprandial glucose. The study enrolled 103 antihyperglycemic agent naïve participants with type 2 diabetes from multiple hospitals in China. The intervention consisted of either nateglinide (120 mg t.i.d.) or acarbose (50 mg t.i.d.) therapy for 2 weeks. The patients were monitored using CGMS to calculate the incremental area under the curve of postprandial blood glucose, the incremental glucose peak, MAGE, and the mean of daily differences. The study results showed that both agents caused significant reductions on the area under the curve of postprandial blood glucose and incremental glucose peak.[4] In conclusion, CGMS provides more information on postprandial glucose levels, glycemic variability and hypoglycemic events when evaluating different therapeutic regimens, which was difficult to imagine before CGMS came onto the market in the old days.

Although the advent of CGMS has provided additional information on glycemic variability, it is still not optimal because of several limitations. First, there are multiple glycemic variability indices assessed from CGM data, such as blood glucose standard deviation, coefficient of variance, interquartile range, MAGE, mean of daily differences and continuous overlapping net glycemic action over an *n*-hour period. Although these indices all represent glycemic variability, they are not entirely consistent, as reported in several studies. Thus, the advantages

Table 1 | Reference values for continuous glucose monitoring parameters in adult Chinese participants

Parameter name	Reference value
Mean blood glucose	<6.6 mmol/L
Percentage of time of blood glucose ≥7.8 mmol/L	<17% (4 h)
Percentage of time of blood glucose ≤3.9 mmol/L	<12% (3 h)
Standard deviation of blood glucose	<1.4 mmol/L
Mean amplitude of glycemic excursion	<3.9 mmol/L

and limitations of each parameter must be studied, so that standard parameters can be established. Second, large follow-up clinical studies exploring the relationship between glycemic variability and relative end-point events in the Chinese population are required to justify the effect of intervention on glycemic variability. Third, by using CGMS, we found that both normal glucose regulation (NGR) subjects and type 2 diabetes patients have experienced blood glucose ≥7.8 mmol/L or ≤3.9 mmol/L (Figure 1). Because of the lack of normal reference data, it was difficult to distinguish profiles of normal glucose and abnormal glucose pattern. Long-term, prospective follow-up studies are required to explicitly define normal reference CGMS parameters. Before that, studies of the typical glycemic patterns in a large sample of continuously-monitored healthy subjects provide a feasible and timely approach to obtain reference values. We previously reported the cumulative time in a day for glucose ≥7.8 mmol/L or ≤3.9 mmol/L was less than 4 and 3 h in NGR subjects, respectively. After excluding minor swings of glucose, defined as less than one blood glucose standard deviation, we found that there were four to five major glycemic swings in NGR subjects in 24 h, and the reference value of MAGE was less than 3.9 mmol/L (Table 1).[5] The Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group also reported relative results in different populations. Therefore, additional studies exploring glucose profiles in NGR subjects are required to establish normal reference CGMS values.

Continuous glucose monitoring as a novel diagnostic technology is still under development in China. Prospective studies involving large patient cohorts are required to validate the long-term efficacy of CGM technology and to determine the population who benefit the most from the use of CGM. Also, its duration of usability, its measurement performance in all clinically relevant glucose ranges and how to make full use of the information provided remain to be determined in the following work. Furthermore, local scholars must carry out detailed health economic analysis to obtain robust cost-effectiveness results. We suggest that all parties involved in the use of CGM cooperate in a constructive manner to optimally utilize this technology.

In the future, real-time CGM will be embedded into the diabetes management process, including routine diabetes education, data analysis and interpretation, and personalized treatment goals in diabetes. All closed-loop systems in development depend on the quality of the CGM measurement. In light of the clear tendency to personalize treatment goals in diabetes, CGM technology will enable both patients and diabetes teams to make better treatment decisions. These decisions might

Table 2 | Examples of studies included the use of continuous glucose monitoring system to evaluate therapeutic effect

Year	References	Participants analyzed	Inclusion criterion	Study duration	Intervention	CGM Parameter end-point
2008	Zhou *et al.*[6] Med Sci Monit 2008, 14: CR 552–558	23 newly diagnosed T2DM	HbA1c >8.5%	2–3 weeks	Multiple daily injections	Significant decrease in MAGE, MODD and AUCpp
2010	Bao *et al.*[3]	40 newly diagnosed T2DM	HbA1c range: 7.0–9.8%	8 weeks	Glipizide controlled-release (CR) vs glipizide CR plus acarbose	Significant decrease in 24-h MBG, MAGE, MODD and AUCpp in glipizide CR plus acarbose group
2013	Zhou *et al.*[4]	103 oral antidiabetic agents-naive subjects with T2DM	HbA1c range: 6.5–9.0%	2 weeks	Nateglinide vs acarbose	Comparably effective in IGP, AUCpp, MAGE, SDBG, MODD and 24-h MBG
2015	Zhou *et al.*[7] Diabetes Metab Res Rev 2015, 31: 725–733	105 patients previously on oral antidiabetic agents	HbA1c range: 7.5–10%	12 weeks	Once-daily insulin glargine plus gliclazide modified release tablet vs premixed insulin	Both therapies reduced the 24-h MBG, but neither reduced MAGE, SDBG and MODD

T2DM, type 2 diabetes mellitus; 24-h MBG, 24-h mean blood glucose; AUCpp, the incremental area under the curve of postprandial blood glucose; IGP, the incremental glucose peak; MAGE, mean amplitude of glycemic excursions; MODD, mean of daily differences; SDBG, standard deviation of blood glucose.

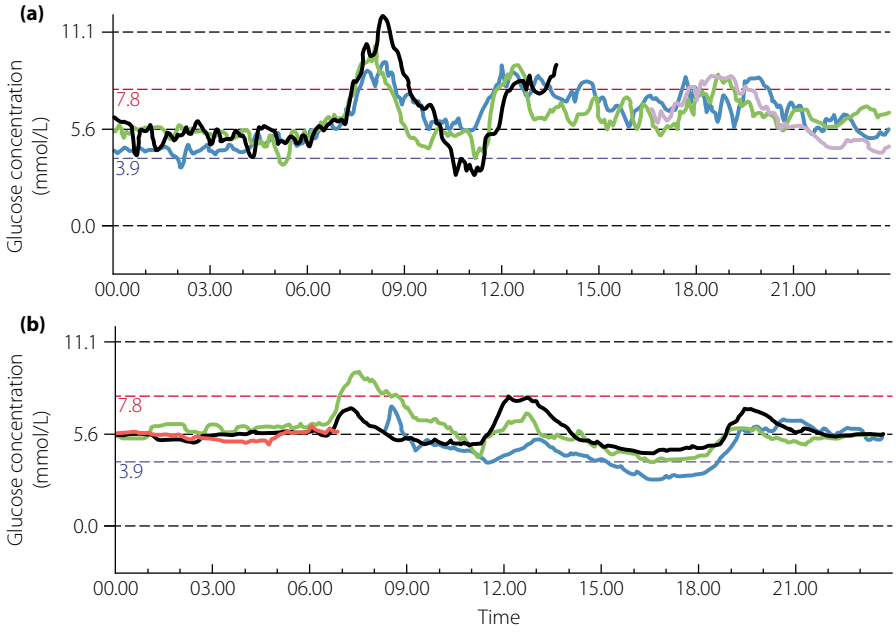

Figure 1 | Continuous glucose-monitoring tracings for 3 days (each day in a different color) in (a) a type 2 diabetic patient and (b) a participant with normal glucose regulation.

increase the frequency of patients who reach glucose control target levels.

Continuous glucose monitoring technology represents a vital advancement in the clinical utility of diabetes technology. Obtaining accurate CGM values provides patients and providers with more information for diabetes care decisions. We believe that CGM technology can serve as another independent glucose monitoring method. This technology will become more than a supplement to SMBG, and could represent a key aspect of diabetes management in the future.

DISCLOSURE

The author declares no conflict of interest.

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