# Continuous Glucose Monitoring

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Editor

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# Foreword 1

Since Banting and Best won the Nobel Prize for their discovery of insulin, there have been many small, iterative advances in diabetes management. However, there have been only a few major breakthroughs that have revolutionized our ability to better control glucose over that same period of time. One of those is continuous glucose monitoring (CGM). Whether used in masked (professional) or real-time (personal) mode, CGM permits the healthcare professional and patient to understand the relationship among the three key elements of metabolic control, i.e., behavior (meals, exercise, stress, etc.), medication (injectable or oral), and glucose levels, in ways not possible with meter-based blood glucose monitoring. CGM is both an educational tool for the patient and healthcare provider (HCP) and a management tool for the HCP regardless of whether the patient has type 1 or type 2 diabetes.

Numerous studies have shown that masked (professional) CGM—essentially a Holter monitor for glucose—adds significant value in the management in both type 1 and type 2 diabetes regardless of whether or not the patient is taking insulin. In addition, it is critical in evaluating the efficacy and safety of not only new pharmaceuticals but also psycho-educational interventions. By the data being masked from the patient the true, real-world effect of the intervention can be determined. Real-time (personal) CGM provides significant information to the patient whether they are receiving insulin by injection or pump. It also has been shown to benefit those with type 2 diabetes not on insulin where it acts as a behavior modification tool.

The future of CGM is discussed in the last chapter. I foresee four major directions in CGM use:

1. CGM will be a bridge to an era when we will use actual glucose metrics (mean, standard deviation, severity of hypo- and hyperglycemia, and times-in-ranges) rather than a surrogate marker (A1C) to evaluate diabetes control. It is well known that there are many problems with using A1C, not the least of which is that there is a wide range of mean blood glucose for a given A1C, e.g., for an A1C of 8% the mean can be from 120 to 200 mg/dL (6.7-11.1 mmol/L) because of different glycation rates, red cell turnover, and other as yet undefined genetic factors. While A1C will remain a touchstone for our understanding of how it correlates with diabetes complications, CGM-derived metrics will permit healthcare providers to make changes between the typical quarterly A1C determination.

2. There will continue to be iterative improvements in CGM accuracy, longevity, and footprint with the use of optical, fluorescence, and hydrogel technologies that permit miniaturization and prolongation of sensor life by months to years.
3. CGM drives artificial pancreas systems. Indeed, we have just entered that era with the US FDA's approval of the MiniMed Medtronic Hybrid Closed Loop system (670G), which automates basal insulin delivery and suspends insulin delivery based on CGM data. Many groups around the world are actively investigating novel algorithms as well as ways to incorporate other relevant hormones like glucagon, pramlintide, and exenatide into artificial pancreas systems.
4. CGM will be used to assess dysglycemia in patients without diabetes including those with prediabetes and obesity, and it is possible that CGM-derived criteria for the diagnosis of these metabolic disorders will be created to supplement the traditional criteria. CGM is likely to be used to educate nondiabetic yet dysglycemic patients about how to modify their lifestyle behaviors. It is also reasonable to think that CGM will be used in wellness efforts by a wide spectrum of individuals without metabolic abnormalities.

Professor Jia and her colleagues have been international leaders in the use of CGM. Their multiple publications in leading scientific journals have provided important insights about diabetes both in China and internationally. Importantly, they have used CGM to establish norms for the population and published one of the first guidelines in how CGM can be used to benefit patients with diabetes and related conditions. This book provides a comprehensive description of the science and clinical use of CGM by one of the world's experts in CGM and is essential reading for anyone treating patients with diabetes.

Robert A. Vigersky
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# Foreword 2

Various types of diabetes with different etiologies or pathogenesis share a common pathophysiological feature, that is, the elevation of blood glucose levels. For more than half a century, measurement of venous or capillary glucose levels or glycated hemoglobin has been the major methods to monitor impaired glucose metabolism. Recent years have witnessed the rapid development of continuous glucose monitoring (CGM) technology, which detects glucose in subcutaneous interstitial fluid through a specialized sensor. As is known to all, blood flows from the capillaries to the veins, and interstitial fluid acts as a bridge in the diffusion of glucose between capillaries and cells of the tissue. Elevation of glucose levels in interstitial fluid, due to impaired glucose uptake or excessive glucose release into the interstitial fluid, represents the basic pathogenesis of the increased plasma glucose concentration in diabetes mellitus. Therefore, understanding intraday and interday trends of interstitial fluid glucose is the stepping stone to in-depth comprehension of normal or impaired glucose metabolism and the metabolism of glucose-related substances. From a hundred years ago when urine glucose testing was initially performed to now, the feasible means for daily routine monitoring of abnormal glucose metabolism remain imperfect and are still in progress.

The evaluation of the accuracy of CGM shows that the technology can reflect the trend in blood glucose fluctuations. Thus, in China, CGM was once referred to as dynamic glucose monitoring technology. CGM helps to understand the trend in glucose fluctuations, as well as to detect occult hyperglycemia and hypoglycemia, which are usually not detected by traditional glucose monitoring methods. Therefore, CGM allows more precise management of diabetes by controlling hyperglycemia, reducing hypoglycemia events, decreasing glucose fluctuations, and finally preventing the occurrence and development of diabetes complications that jeopardize the health and life span of patients.

The technology of CGM is among the great achievements of glucose monitoring technologies for diabetes. Since 1999 when the retrospective CGM system was first launched, CGM technology has played a positive role in promoting progress in diabetes management. In order to expand the knowledge of CGM technology and to facilitate the scientific, standardized, and reasonable use of CGM technology, the authors compiled this book based on their long-term original researches and clinical experience, as well as the scientific findings from domestic and international counterparts.

The authors of this book introduced their initial work on the establishment of the normal reference ranges for CGM parameters in Chinese population. Indeed, the definition of the "normal" value is the key to judging "abnormalities." In the early years of clinical application of CGM technology, there was a lack of normal reference values for CGM parameters and the reference range of finger-stick glucose value was apparently not suitable to CGM measurements. These limitations significantly hindered the interpretation of CGM results and the clinical application of this technology. Previously, the authors carried out a multicenter study and obtained large amounts of normal CGM data and established the CGM normal reference range for the first time worldwide. In the book, the authors introduce their innovative work and compare and analyze similar findings from domestic and international counterparts in different ethnic groups. These studies lay the foundation for scientific application of CGM and rational explanation for CGM results, and solve the key problems in making the best use of CGM technology in clinical practice.

Moreover, the authors introduce their CGM reporting and management system in details, which was developed independently with intellectual property rights. Scientific interpretation of CGM data and its graphical display are important to the clinical use of the technology as are the presentation of a comprehensive display of glucose metrics and standardized reports. By illustrating clinical cases, the authors introduce their CGM reporting system and explain how to interpret or analyze CGM profiles. Their reporting system includes an analysis software, which can calculate CGM-derived metrics and generate a standardized CGM report automatically. All these efforts enable clinicians to understand the trend of blood glucose fluctuations in patients.

Furthermore, the clinical significance and application of CGM metrics proposed by domestic and international scholars are reviewed in the book. The authors also summarize the advantages and concerns of several parameters based on the clinical trials conducted by themselves.

In the book, the current clinical application of CGM technology is discussed in detail. The book also demonstrates the use of CGM measurements in various situations of abnormal glucose metabolism, as well as the role of CGM in evaluating the efficacy of different hypoglycemic therapies.

I would like to thank my colleagues in Shanghai Clinical Center for Diabetes who have engaged in glucose monitoring studies and related clinical work for their persistent devotion and efforts to promote the development of CGM in China. It is expected that this book will help all the readers gain a comprehensive understanding of the CGM system and promote the standardized and wide application of CGM in clinical practice, thereby contributing to the improvement of diabetes management in China.

Shanghai, China Kunsan Xiang

# Preface

Blood glucose monitoring is an important part of diabetes management. It plays an essential role in the assessment of glucose metabolism disorders, thereby guiding the optimization of the magagement of diabetes. As blood glucose level changes continuously, neither the glucose values at certain time points nor glycated hemoglobin reflects the dynamic fluctuations in blood glucose throughout the day. Indeed, the capture of continuous glucose monitoring has always been a dream pursued by both patients and clinicians for a long time. As in the early 1960s, Clark and Lyons first put forward the concept of a glucose sensor. The designed sensor consisted of a thin layer of glucose oxidase (GOD), an oxygen electrode, an inner oxygen semipermeable membrane, and an outer dialysis membrane. The glucose concentration could be calculated by measuring the change in the local oxygen concentrations. In 1967, Updike and Hicks further improved the detection assay and measured glucose concentrations in biological fluids of an animal model for the first time. Subsequently, continuous glucose monitoring (CGM) technology has become increasingly sophisticated and accurate and has been gradually promoted from the experimental monitoring to clinical application.

In 1999, a CGM system was approved by the US Food and Drug Administration (FDA) for clinical use, allowing a convenient, panoramic view of all-day changes in blood glucose for the first time. Since 2005, the real-time CGM system has been applied in clinical practice. In addition to real-time display of monitoring results, it integrates alarm and predictive alert features, providing a guarantee for the safety of treatment. At the same time, the development of CGM technology promotes the creation of algorithms that can modify the rate of continuous insulin infusion. Moreover, with the application of CGM technology, investigators have been able to study the normal patterns of glucose variation and how they differ under different clinical circumstances.

In 2001, we started to apply CGM in clinical practice in China for the first time. We found some challenges that need to be addressed. For example, the lack of normal reference range for CGM parameters, the absence of standardized interpretation methods for CGM graphs, and the complex and time-consuming process of CGM data analysis. In addition, little experience exists regarding the clinical indications for this new technique, the methods for assessing the accuracy of CGM data, and how the data should be used to guide decisions in clinical practice. To address these challenges, we established the normal reference values of CGM parameters by a national multicenter study, which was the first reported evidence domestically and internationally. We also analyzed the patterns of blood glucose fluctuations in different metabolic disorders, carried out standardized protocols for CGM graphs interpretation, and designed a series of supporting software and management systems independently to simplify the time-consuming data analysis process. We have published more than 50 papers related to CGM in domestic and international journals, established a CGM database containing more than 15,000 cases, and accumulated a wealth of clinical experience. In order to further enhance the knowledge of CGM technology among professional medical staff in the fields of endocrinology and metabolism, we have compiled this book to facilitate the scientific, standardized, and proper utilization of CGM technology.

The book firstly focuses on the basic knowledge of CGM technology, and then introduces the advantages and applications of the CGM system with clinical cases. In the book, we introduce the principles, the operation methods, the management procedures, and indications of CGM. Also, the alarms settings and responses to the alarms, interpretation of CGM results, the analysis of clinical cases, the relative researches and prospects are also discussed. This book is edited mainly based on our original research results and specifically focuses on the clinical application. It illustrates CGM knowledge in the form of clinical cases and graphs, with the aim of becoming a reference book guiding the application of CGM technology in clinical practice and scientific research.

All the clinical trials carried out by the authors in this book have been reported to the Ethics Committee of Shanghai Jiao Tong University Affiliated Sixth People's Hospital already and were in accordance with the Good Clinical Practice and Standards of China Association for Ethical Studies (approval number: 2007-45).

I would like to thank my colleagues in the Department of Endocrinology and Metabolism and Shanghai Diabetes Institute who have engaged in the glucose monitoring and clinical work for years for their continuous dedication. In addition, my colleague Jie Li and graduate students Xingxing He, Hang Su, Lingwen Ying, Jiahui Peng, Lingli Cai, Yiming Si, Dongjun Dai, Yun Shen, and others who have contributed in the careful editing and chart proofing. Specifically, my mentor, the Chinese Academy of Engineering member, Professor Kunsan Xiang, and the former president of the Endocrine Society, Professor Robert A. Vigersky, wrote the foreword for this book. Also, many thanks to my editors Ling Wan, Jianshe Zeng, Lujing Kong, et al. in the Shanghai Scientific and Technical Publishers for their help and support.

There might be some inevitable shortcomings and omissions exist in the book. We sincerely hope that readers will share their valuable advice and suggestions for future improvements.

Shanghai, China — Weiping Jia

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# About the Editor and Associate Editors

**Weiping Jia** is a Chinese endocrinologist, professor of medicine at Shanghai Jiao Tong University, president of the Shanghai Sixth People's Hospital, director of the Shanghai Clinical Center for Diabetes, and director of Shanghai Diabetes Institute. Professor Jia also serves as the president of Chinese Diabetes Society, chief editor of the *Chinese Journal of Internal Medicine*, associate editor of *Diabetes Research and Clinical Practice*, as well as an editorial board member of *Lancet Diabetes Endocrinology*. She is the chief editor of the *Chinese National Guideline for Prevention and Treatment of Type 2 Diabetes Mellitus (2017 Edition)* and the *Chinese National Guideline for Primary Healthcare of Diabetes (2018 Edition)*. Her research interests include the diagnosis and monitoring of diabetes as well as identification of genetic risk factors for diabetes. She established new diagnostic standards for diabetes and abdominal obesity, discovered novel T2DM genetic susceptibility loci, and established normal reference values for continuous glucose monitoring in Chinese population. She has published over 100 research articles in international journals, including *Diabetes*, *Diabetes Care*, *Diabetologia*, *JCEM*, *BMJ*, *Lancet Diabetes Endocrinol*, and *JACC*. Her research has been funded by the Natural Science Foundation of China (NSFC), the National Basic Research Program of China, and the European Association for the Study of Diabetes (EASD). She is the Co-PI of research projects funded by the US National Institute of Health (NIH). Since 2015, she has been the PI of the Construction of Prevention and Treatment of Diabetes Healthcare System in Shanghai, the largest community-based screening program for complications of diabetes in China which covers over 200,000 patients.

**Jian Zhou** is the associated professor of medicine at Shanghai Jiao Tong University and the deputy director of the Department of Endocrinology and Metabolism, Shanghai Jiao Tong University Affiliated Sixth People's Hospital. He also serves as the member of the Youth Committee of Chinese Society of Endocrinology, the secretary and committee member of Shanghai Diabetes Society, an editorial board member of *Cardiovascular Diabetology*, and the corresponding editor of *Chinese Medical Journal, Chinese Journal of Endocrinology and Metabolism*, and *Chinese Journal of Diabetes*. His career has focused on diabetes and obesity, and he has taken the leading role in promoting the new technology of Continuous Glucose Monitoring in China. He was the first researcher who proposed to establish the normal reference values of Continuous Glucose Monitoring parameters and published the relevant results in Chinese population on *Diabetes Care*. He has published more than 90 research articles (as first or corresponding author), among which 30 were cited by international peer-reviewed journals.

**Yuqian Bao** is a Chinese endocrinologist, professor of medicine at Shanghai Jiao Tong University, the director of the Department of Endocrinology and Metabolism, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, and the executive deputy director of Shanghai Clinical Center for Diabetes. She also serves as the vice chairman of Specialty Subcommittee of Diabetes Prevention and Control of Chinese Preventive Medicine Association, member of Chinese Society of Endocrinology, and the president of Shanghai Diabetes Society. Her career has focused on obesity, and she was professionally trained in key research areas.

Her team established the accurate diagnostic criteria of central obesity (abdominal obesity) for the first time in Chinese population and defined the corresponding waist circumference cutoffs, which were adopted by the "Criteria of weight for adults" (WS/T 428-2013) issued by National Health and Family Planning Commission of the People's Republic of China in 2013. She was also the first researcher who proposed to use glycated hemoglobin A1c as a supplemental index for the diagnosis of diabetes in Chinese population and published the relevant results in the *British Medical Journal*. Moreover, she has established the hyperglycemic clamp technique as the precise method to evaluate pancreatic β-cell function in Chinese population. In recent years, her team has founded a model of comprehensive management of metabolic surgery, also called the "Shanghai Model" by local and international researchers.

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