Maturation of CGM and Glycemic Measurements Beyond HbA_{1c}—A Turning Point in Research and Clinical Decisions

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Periodically, a new idea, method, or tool leads to a turning point in the management of diabetes. We believe such a moment is now upon us, brought by development of reliable devices for continuous glucose monitoring (CGM). Obtaining profiles of glucose levels continuously, day and night, is likely to bring new scientific insights and greater ability to individualize treatments for patients with both type 1 diabetes (T1D) and type 2 diabetes (T2D). Notably, such profiles provide the opportunity to develop measures of glycemic control that provide clinically helpful information beyond that provided by an HbA_{1c} value and periodic self-testing of capillary glucose. Several articles in this issue of *Diabetes Care* summarize recent progress in CGM measurements and their interpretation. The editorial committee of *Diabetes Care* is proud to present a Scientific Statement developed jointly by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes titled "Improving the Clinical Value and Utility of CGM Systems: Issues and Recommendations" (1). This statement reviews clinical evidence regarding use of CGM and describes the properties and limitations of available CGM systems. It also addresses some practical issues regarding instruction of potential users of these devices and concerns about safety. In addition, we present two other Consensus Reports. In one, experts representing various groups with a strong interest in T1D define measures of glycemic control other than HbA_{1c}, including categories of hypoglycemia and proportions of time in glucose target ranges during CGM, and also consider how best to use patient-reported outcomes in T1D (2). A strong consensus reached by these groups provides an important step forward from previously differing approaches to these issues. In the other, an international group of experts reviews current evidence on how best to use CGM information for improving patient care and research, including a discussion of the need for standardizing the format by which data are reported using different CGM systems (3). Although there is some overlap of topics and opinions between these articles, each one emphasizes different aspects. Several related studies and narratives are also included in this issue of *Diabetes Care* with a special emphasis on CGM and hypoglycemia (4–7).

Beyond their enthusiastic agreement on the potential value of CGM, the three main articles (1–3) agree on two important points. First, they all favor standardization of definitions of terms and ways of reporting the findings of CGM. Second, they all support refining the classification of hypoglycemia to include three main categories: severe events requiring assistance, clinically important events with values lower than 54 mg/dL (3.0 mmol/L), and events with values between 54 and 70 mg/dL (3.0 and 3.9 mmol/L), which may be regarded as warning signals for more serious events. Consensus on the classification will simplify comparison of the effects of glucose-lowering therapies across different drugs and a range of patient characteristics. Standardized data collection and reporting may then open the door to a paradigm shift in regulatory assessment of therapies, to include hypoglycemia as a relevant and reliable consideration.

Notwithstanding their strengths, these statements do not address other important questions. For which patients should CGM be prescribed and reimbursed? How can those who use CGM learn to do so most effectively? What glycemic goals are attainable for various kinds of patients? How do we determine the levels and frequencies of hypoglycemia that are safe and tolerable for individual patients? These unanswered questions highlight limitations of knowledge about the devices themselves and also about how daily glycemic patterns contribute to the complications of diabetes and the risks associated with treatment. Fortunately, because CGM can be both a clinical guide and a unique tool for clinical

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investigation, research questions that were previously out of reach can now be studied. One research question that is relevant to individualization of therapy has already been partly answered. The hypothesis that Caucasian and African American populations may differ in the relationship of HbA_{1c} to mean glucose levels has been supported by data collected by CGM (8). Differences between individuals within ethnic groups are also apparent (9), and CGM findings may be used to establish an individual's unique HbA_{1c} target based on that person's HbA_{1c}–to–mean glucose relationship.

Glycemic variability is another aspect of metabolic control for which there has been inadequate evidence of clinical relevance. The hypothesis that glycemic variability contributes to microvascular disease or atherogenesis beyond the effects of mean hyperglycemia (10) can now be tested by analyzing the results of CGM among a set of risk factors. Furthermore, the relation of hypoglycemia to cardiovascular events and mortality can at last be systematically studied. For example, in T1D, it is known that hypoglycemia can be associated with cardiac arrhythmias (11), but strong evidence on the frequency of such events or the magnitude of the relationship to sudden death is lacking. In T2D, severe hypoglycemia is associated with increased risk of death, but whether it is a cause as opposed to a marker of risk is unknown (12,13). Cardiovascular outcome trials in which CGM is systematically used may provide the answers.

Another exciting possibility is that CGM can be used as an outcome measure in clinical trials. Up until now, comparisons of hypoglycemic risks in clinical trials have been limited by the fact that many events are unrecognized and therefore not reported by the patient. Documentation of unrecognized events in trials depends on the frequency and timing of glucose testing, which may differ between randomized groups, introducing bias in assessing the true incidence and rate of events. A particular problem concerns the use of 6-, 7-, or 8-point self-measured glucose profiles to assess preprandial, postprandial, and overnight patterns and the frequency of events. Because few people eat their meals at the same time each day, the results of these standardized profiles may bear little relation to a patient's actual day-to-day patterns. Continuous measurement of glucose eliminates this problem and additionally reveals between-day differences as well as within-day patterns of glycemia. Availability of better data regarding these research questions may facilitate regulatory evaluation of new therapies and may support constructive changes in guidelines for management.

Finally, CGM has several potential clinical uses. Its use to "close the loop" by linking ongoing glycemic trends directly to insulin delivery systems is a leading goal. In this issue of *Diabetes Care*, Breton et al. (4) report experimental use of a closed-loop system during vigorous exercise by a small group of young people with T1D, with encouraging results. However, despite improved accuracy and durability of glucose sensors, better pumps, and more refined algorithms for insulin adjustments, closed-loop systems are still investigational rather than part of routine care. Another attractive feature of real-time CGM is its potential to limit severe hypoglycemia by providing an early warning. Already there is evidence that patients at high risk for severe hypoglycemia may benefit from CGM (14), and current devices are likely to be vigorously marketed with this rationale.

However, the proportion of patients at high risk of severe events is not large and mainly limited to T1D. In this issue, Zhong et al. (5) report a retrospective analysis of incidence and trends for hypoglycemia resulting in hospitalization in the U.K. They found that between 1998 and 2013, a population of over 23,000 adult patients with T1D had 1,591 such events, while more than 240,000 patients with T2D had 3,738 events. Whereas these numbers of events are not trivial and deserve attention, the majority of patients never had an event of this kind over 15 years of observation. Nevertheless, many of them might still benefit by using CGM to facilitate decisions in insulin dosing and other aspects of management, with the aim of safely improving glycemic control. Also in this issue, Lee et al. (6) report the frequency of hypoglycemia requiring assistance during 15 years of careful, prospective follow-up of 1,206 patients, most with T2D. A total of 185 such events were reported, again demonstrating that most patients did not have any events. As in other studies, risk factors for severe events included older age, poor glycemic control, high glycemic variability, and impairment of renal or cognitive function (6). Very likely, some of those identified at high risk by these characteristics could be protected by use of CGM, while some of those at lower risk might use CGM to improve glycemic control. Prospective studies of both kinds of patients would be helpful.

We also have not defined in detail how the potential benefit of CGM can best be translated to action. Among other concerns, selection of an individualized target for HbA_{1c} and for a tolerable degree and severity of hypoglycemia is not always straightforward. This point is highlighted by a Perspective in this issue of *Diabetes Care* by Philip E. Cryer (7), which advocates a definition of severe events that is slightly different from that proposed in the previously described Consensus Reports. Influenced by concern about high risks associated with hypoglycemia unawareness, Cryer suggests that any measurement of glucose $<$50 mg/dL (2.8 mmol/L) should be considered a severe event, independent of whether symptoms were present or assistance by another person was required, and presumably calling for an immediate change of therapeutic tactics. For some individuals, this is a powerful argument, but not all patients with a single measurement in this range are likely to have the same level of future risk. Determination of the risk associated with one or several values below this level (or $<$54 mg/dL [3.0 mmol/L]) in different clinical settings can only be clarified by further clinical studies using CGM.

The way CGM is used to make adjustments to insulin dosing also may require individualization. The simplest part of intensive insulin therapy is basal insulin dosing, which can be optimized by viewing overnight and fasting glucose and adjusting accordingly. For this decision, CGM is often not needed. Unfortunately, management of mealtime insulin is more difficult. Premeal bolus doses must be chosen before the meal is eaten, and many features of the meal are relevant. Total carbohydrate is just one variable, with additional contributions from how the meal is prepared; its content of fiber, protein, and fat; the order in which components of the meal are eaten; whether any exercise precedes or follows the meal; and even the time of day. Decisions regarding correction doses when hyperglycemia occurs before or between meals are even more problematic. More insulin is

needed to reduce hyperglycemia than to prevent it, and the sensitivity of tissues can be reduced by hormonal responses to hypoglycemia occurring up to 12 h previously. Standardized algorithms for insulin dosing are not always reliable, and it is unclear whether CGM will lead to improved decisions. Indeed, for some patients, the greatly increased volume of data provided by CGM may prove to be overwhelming.

For all these reasons, instruction, advice, and support provided by a physician or other provider experienced in intensive diabetes management remains essential when applying CGM data to individualize and enhance therapeutic tactics. Because optimal use of CGM may require more rather than less advice and support, cost-effective use of CGM will require defining specific groups of patients who benefit the most. The experience of patients using CGM must remain a central concern, with ways to improve education and satisfaction explored to obtain the greatest return on this investment of time and resources. Guidance as to which patients should use CGM, how they can best be advised and supported, and how to individualize their glycemic goals will depend on the results of CGM-based research.

Given the above, the next question is who will provide this guidance. The statements presented in this issue of *Diabetes Care* represent a very good start by demonstrating greater consensus on definitions and by posing the next set of research questions. But they are not the end of this process. Further independent review of data by professional groups (such as the ADA and others) and governmental groups (including the U.S. Food and Drug Administration) will be necessary. Health care providers, health systems, and consumer groups will also have to participate. All these groups will require objective data from ongoing and future research using CGM to formulate their guidelines and expectations. This is a current version of an old process, in which unmet clinical needs lead to new scientific insights and therapeutic tools, followed by clinical testing of these tools in everyday clinical settings, and finally leading to reliable guidance for practice. We are now entering the phase in which clinical research will address the remaining questions about how CGM can add clinically useful information that is not provided by HbA_{1c} or self-measured capillary glucose. *Diabetes Care* will continue to welcome results from studies of these issues, ask newly relevant questions, and disseminate this information to the diabetes community.

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