

State of the Art: Continuous Glucose Monitoring

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INTRODUCTION

Fourteen years after the publication of the Diabetes Control and Complications Trial (DCCT) results (1), the majority of patients with type 1 diabetes do not meet recommended glycemic control targets. The pediatric population presents unique challenges. Recent implementation of technological advances in the management of pediatric type 1 diabetes creates an exciting time for the diabetes community. Safety and efficacy of new therapies are commonly demonstrated first in adult patients with pediatric studies following. Continuous glucose monitors (CGM's) have shown, in preliminary studies, the potential to improve glycemic control in adults and children. Advances in technology assist us to more closely mimic normal physiology, thereby achieving improved glycemic control, leading to fewer acute and chronic diabetes complications. In addition, technological advances will allow our patients to achieve intensive management with improved quality of life, more flexibility, and fewer burdens. Here we will describe the current state of the art, a large study of CGM's being funded by the Juvenile Diabetes Research Foundation (JDRF), challenges in applying these new tools in practice, and gaze toward the future of closed-loop automated insulin delivery.

GLUCOSE MONITORING

Successful management of type 1 diabetes in children and adolescents requires the coordination and balance of multiple, and sometimes, unpredictable variables. Children and their caregivers must take into account variations in the timing, composition, and size of meals and duration, intensity, and type of physical activity when they are adjusting insulin doses. Self-monitoring of blood glucose is one tool that assists the patient or caregiver most readily in making these treatment decisions. However, blood glucose

monitors, provide only episodic data and do not provide information on the rate and direction of change in the blood glucose concentration. CGM is a recent technological advance that provides real-time blood glucose data every 5 minutes (every 1 minute in some models), allowing the patient and the healthcare provider to track blood glucose throughout the day. This technology will provide detailed information about blood glucose fluctuations: extent, duration, and frequency of hyper- or hypoglycemia; relationship of excursions in blood glucose to certain activities or foods; and trend data to help the individual predict and possibly prevent periods of hyper- or hypoglycemia. In addition, CGM is the first step in closing the loop for an artificial pancreas.

Continuous glucose sensing provides opportunities for improved glucose control in three arenas. First, it provides alarms for high and low glucose values. Second, it provides a means for real time insulin adjustments based not only upon the glucose value but whether the blood glucose is rising, falling, or stable at that moment. Third, continuous glucose sensing allows a retrospective review of glycemic excursions based upon time of day, activity level, and food intake that can be used to refine insulin adjustments. Potential advantages also include less frequent and less severe hypoglycemia. A study by Garg et al. evaluated the safety and efficacy of the DexCom STS™ device, using the original short-term (72 hr) real-time continuous glucose-sensor (STS System; DexCom, San Diego, CA) (2). Use of this sensor was associated with a decreased amount of time spent in hyper- and hypoglycemic ranges while increasing the time in the euglycemic range. Diess et al. (3) showed in children and adults that patients utilizing CGM (the Medtronic Guardian RT) achieved a significant A1c reduction without addi-

tional hypoglycemia. Bailey et al. (4) demonstrated similar A1c reductions in adults utilizing the DexCom sensor.

There are currently two FDA-approved manufacturers of real-time continuous glucose sensors for use in adults 18 years of age and older and one awaiting approval, one device is FDA-approved for use in children ages 7-17. The DexCom STS™ Continuous Glucose Monitoring System was approved in March 2006. The wireless sensor device determines glucose levels in subcutaneous tissue and radio transmits glucose data to the receiver every 5 min for up to one week with a recently approved sensor. MiniMed offers the only CGM devices currently approved for use in children, one is a stand-alone device and one is coupled to an insulin pump although the glucose data are not used to dose insulin. The MiniMed Paradigm® REAL-Time System (approved April 2006) communicates with the Paradigm 522/722 pumps and the MiniMed Guardian® Real-Time System (approved July 2006) communicates with a separate monitor. Both systems transmit blood glucose data every 5 minutes for up to 72 hours. The Guardian® Real-Time System alarms when the sensor predicts a low or high blood glucose based on the latest sensor glucose and rate of change and also alarms for a rapid rate of change in glucose. Finally, the Freestyle Navigator™ (Abbott Diabetes Care, Alameda, CA) is a 5-day real-time continuous glucose monitor awaiting FDA approval. The Navigator™ displays blood glucose values every minute with the direction and rate of change also displayed. The Navigator uses vector technology to alarm up to 30 minutes before it predicts the occurrence of a low or high glucose target. Currently, no sensors are approved as replacement for traditional blood glucose monitoring.

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Questions regarding the safety, accuracy, and psychological impact of continuous glucose monitors in the pediatric population remain. It is possible that CGM will reduce anxiety about hypoglycemia, but it may also increase anxiety when the continuous glucose monitor data and results from traditional self-monitoring do not agree. In addition, the amount of blood glucose data may overwhelm a patient and family and increase the burden of diabetes management. The Diabetes Research in Children Network (DirecNet) Study Group recently published data on the psychological outcomes from a randomized trial of the GlucoWatch G2® Biographer (Cyngus, Inc., Redwood City, CA) (5). Results from surveys measuring diabetes treatment adherence, diabetes-specific quality of life, and diabetes-related anxiety demonstrated that there were no adverse nor beneficial psychological effects of CGM using the GlucoWatch G2® Biographer. However, the GlucoWatch differs enough from the other currently available technologies such that the results from this trial may not be transferable to other sensors.

THE FUTURE

Recently the JDRF launched a large multicentered randomized controlled trial to test the effectiveness of continuous glucose sensors in children and adults. The study is powered to detect a reduction in A1c after 6 months of CGM use in patients with an initial A1c above 7.0%. Additionally, a second cohort of patients who enroll with A1c levels below 7% will be monitored for hypoglycemia reduction. A number of other outcomes will be captured for all study participants, including measurements of time spent hypo- and hyperglycemia, glycemic variability, clinical hypoglycemic events, and a number of metrics of quality of life. Devices from all three of the manufacturers described above are being utilized. We expect another outcome of this trial to be the development of implementation and dissemination tools and algorithms for optimized use of CGM's. The "holy grail" of diabetes technologies would be an automated fully closed-loop insulin delivery system that would regulate blood sugars like the beta cell. The limitation in developing such a system has been the lack of a robust continuous glucose monitor and a mature control algorithm that

would drive the insulin delivery system. Today, as we have described, the former is rapidly maturing to the point of potentially being robust enough to drive such a system. In parallel to the study described above, the JDRF is currently funding a consortium of diabetologists, engineers, and mathematicians to develop and test the latter – the control algorithms. Encouragingly, the preliminary results are extremely promising. Using "off the shelf" components – in this case a Medtronic CGM and Pump – a group led by Dr. Stuart Weinzimer at Yale has shown excellent feasibility data of a fully closed-loop system in teens with type 1 diabetes within the GCRC. Work is rapidly evolving and points to an exciting time where some degree of insulin delivery may be automated.

CONCLUSIONS

The evolution of glucose monitoring from urine testing to single point capillary blood glucose to continuous interstitial glucose measurement provides us with amazing opportunities to normalize blood glucose, but also with considerable challenges to handle data, obtain reimbursement, and train patients and providers alike in sensor use and trend interpretation. These technological advances offer patients, families, and healthcare providers with new approaches to managing pediatric type 1 diabetes with the potential for improved glycemic control and quality of life. The next 10 years will hopefully bring additional technological advances that will close the loop for an artificial pancreas and approach a cure for type 1 diabetes.

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