Feature Article

Diabetes Technologies and Their Role in Diabetes Management

Sobha Kollipara, Janet H. Silverstein, and Katie Marschilok

ABSTRACT

The 1993 Diabetes Complications and Control Trial (DCCT) showed that controlling blood glucose prevents and delays the progression of long term complications of diabetes. New diabetes technologies can make control of diabetes possible and safer. This paper reviews these technologies used to monitor blood glucose, administer insulin and evaluate effectiveness of therapy. Self-monitoring of blood glucose has been a standard of care for several decades. Today, patients and practitioners can gain great benefit from data that can be provided by using Continuous Glucose Monitoring (CGM). Current physiologic insulin therapy regimens have improved blood glucose control capabilities. Insulin therapy devices; including pens and pumps are reviewed. Advantages of insulin pump therapy and features of the latest 'smart' pumps are described. Children with diabetes, and their families, have many challenges as well as many opportunities to employ new technologies in diabetes management plans. The ability of school and care givers to support children can impact the overall success of any diabetes therapy regimen.

Kollipara S, Silverstein JH, Marschilok K. Diabetes technologies and their role in diabetes management. Am J Health Educ. *2009;40(5):292-297. This paper is part of a sponsored set of papers contributed through the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health.*

INTRODUCTION

The control of diabetes and its effects on long-term morbidity are well known. Many new ideas and modalities have been explored that target improved methods to monitor blood glucose and deliver insulin to achieve better metabolic control. Over the years, technological advances in these areas have made it possible to improve blood glucose control. This review addresses these newer technologies such as:

- Blood glucose (BG) monitoring
- Real time continuous glucose monitoring (CGM)
- Insulin delivery with insulin pens and pumps
- The closed loop system (artificial pancreas)

• Blood Glucose Monitoring

Blood glucose monitoring as a means of assessing diabetes control has been used since the 1970s and is an essential clinical tool in day-to-day diabetes management. The Diabetes Control and Complication Trial clearly has shown that good control of BG improves short- and long-term microvascular complications.[1] Because of technological advances, the devices that monitor blood glucose are more accurate and efficient than ever before.

BG monitoring is done using two methods: blood glucose meters for checking blood glucose levels at discrete times, most commonly used for day-to-day diabetes management; and continuous glucose monitoring.

Blood glucose meters. Self-monitoring of blood glucose (SMBG) is the essence of day-to-day diabetes control. SMBG enables patients and their health care providers to make medication adjustments that achieve and maintain optimal glycemia. Over the

Sobha Kollipara is the director, Pediatric Endocrinlolgy and Diabetes, Kaiser Permanente Roseville, Roseville, CA 95611; E-mail: sobha.kollipara@kp.org. Janet H. Silverstein is a professor and chief in the Pediatric Endocrinology Department, University of Florida, Gainesville, FL 32608; E-mail: silvejh@peds.ufl.edu. Katie Marschilok is a diabetes clinical manager, Medtronic Diabetes, 4 Fairlawn Lane, Troy, NY, 12180; E-mail: katie.k.marschilok@medtronic.com.

last decade, glucose meters have dramatically improved in their ease of use, in time required to perform the test and in volume of blood required.

Technology of the glucose meters. All glucose meters use enzymes that oxidize the glucose in the blood sample. Electrons released from the glucose by this reaction generate an electrochemical current that is measured as a digital value displayed on a screen. The amount of current released is proportional to the glucose concentration. Most of the meters use this method for glucose measurement. Though most of the meters contain sensors that adjust and correct to the outside temperature, glucose strips used for meters may give inaccurate readings in extreme hot or cold weather. It is advisable to wait before testing to assure that strips are at room temperature, to eliminate errors.

Accuracy and precision. All glucose meters in use today are reasonably accurate, with blood glucose values being within 5% (5mg/dl <100mg/dl) of the lab value if done with capillary blood from the finger. There is also good reproducibility, with blood glucose results from the same drop of blood on two separate occasions having little variability, differing by only 2% to 3%.[2] The difference in readings between two meters using the same drop of blood has been shown to be less than 4%.[3]

Most meters need only about 0.3 to 10 µl of blood to function. Most current meters are calibrated for capillary blood from finger tips. There is an increasing demand for testing at alternate sites because of the discomfort of the frequent finger pricking. Some meters are FDA approved for alternate site testing with the forearm being the most popular site, though the abdomen, thigh and other areas of the body may be used. However, there are limitations to the use of alternate sites. There is lag time between the actual blood/capillary glucose (finger prick) to that of interstitial (other sites), resulting in delayed recognition of hypoglycemia.[4] Accuracy of the level is affected for the samples obtained after exercise and one-hour post-prandial (after a meal), especially if glucose levels are low.[5]

Data storage and reproducibility. All meters are equipped with memory of data storage in many different formats. In addition to the blood glucose data, other information such as food and exercise data can be stored. These stored data can be imported into patient's charts using software for uploading, transmitted to insulin pumps and communicated to health care providers via web-based programs. The computer data displays are used to estimate the glucose trends; average and standard deviations that help to identify insulin adjustment needs. The new glucose meters are easy to use resulting in improved patient acceptance and motivation to improve diabetes control.

CONTINUOUS GLUCOSE MONITORING (CGM)

Continuous glucose monitoring recently has been approved by the FDA and provides an additional tool for diabetes management. These monitoring devices are approximately the size of a cellular phone and are worn on a belt or in a pocket. A sensor is inserted through a plastic cannula under the skin, in the subcutaneous tissue. Glucose values are displayed on a digital screen every few minutes with arrows or other indicators of blood glucose trends, allowing the adjustment of food or insulin early to prevent low or high blood glucose levels. Several FDA approved devices are available commercially for continuous glucose monitoring. However, these devices are complex, and specially trained diabetes care personnel are needed to teach patients how to use them.

Technology of CGM. All commercial CGM devices measure glucose from the interstitial subcutaneous tissue. The sensors generally are stable and functional for 3 to 7 days. The system consists of a transmitter which provides the energy for the sensor and facilitates the transfer of the glucose signal to a receiver. The sensor takes time to generate an accurate signal after insertion, and it is important to recalibrate if the sensor is detached for any reason. Currently there are four such CGM devices (Table 1).

All sensors can be programmed for low and high alarms that are set by parents, and all indicate that action must be taken. Glucose values are recorded every five minutes. Sensors measure a wide range of glucose levels, from 20mg/dl to 500 mg/dl. All involve wireless transmission of data to a receiver.

Accuracy of the sensor data. Because the glucose levels that these sensors measure are of the interstitial tissues, readings from the BG meter differ from the sensor glucose levels by 8mg/dl to 18 mg/dl. There is a time lag between measurements—the sensor value reading lagging behind the meter reading.[6] Whenever rapid or wide fluctuations in blood glucose levels occur, there is an even greater difference between the sensor value and finger stick BG value. For these reasons, calibration should not be performed following meals or during hypoglycemia. Sensors should be calibrated using the capillary levels obtained on the glucose meter a few times over a 24-hour period.

The most useful information that the sensor provides is about trends of glucose excursions, which can be used to make appropriate changes in insulin dosing, food intake and physical activity. Sensors have been tested in studies to test patient acceptance,[9] ability to lower HgbA1C[7] and ability to detect hypoglycemia.[8] A large study is underway to test the effect of these sensors on diabetes control.

Sensor and hypoglycemia. Avoidance of clinically significant hypoglycemia is important because low blood glucose levels have negative effects on health. CGM has helped in identifying and reducing the frequency and degree of hypoglycemia. To detect low BG values, the sensor alarm can be set for specific glucose levels and for the glucose level rate of fall. Thus, based on the rate of fall of glucose, potential hypoglycemia can be prevented. Patients who use the sensor feel that it helps decrease the frequency of hypoglycemia and gives them additional information for adjusting insulin doses. The CGM devices store all blood glucose data and include software that allows the information to be downloaded. This information can be inter-phased with the insulin delivery history from an insulin pump and used to make insulin dose adjustments.

Table 1. Continuous Glucose Monitoring Devices

Features	Medtronic MiniMed Guardian	Medtronic MiniMed Real Time Insulin Pump	DexCom	Freestyle Navigator
Communication	Wireless receiver	Insulin pump receiver	Wireless receiver	Wireless receiver
Distance	6 feet	6 feet	5 feet	10 feet
Sensor life	3 days	3 days	7 days	5 days
How BG data are obtained	Manual or linked to glucometer	Same as the Guardian	Cable link to One Touch Ultra or manual	Freestyle meter built into the receiver
Number of calibrations	2 to 4 / day	2 to 4 /day	2 to 4 /day	4 / 5 days
Predictive high/ low alarm	Yes	Yes	Yes	Yes
Range of glucose display (mg/dl)	40 to 400	40 to 400	40 to 400	20 to 500
Display updated	Every 5 minute	Every 5 minutes	Every 5 minutes	Every 1 minute
Events that can be entered	Insulin, meals, exercise	Insulin, meals, exercise	None	Insulin, meals, exercise, health, other
Computer software	Insulin, meals, exercise, Carelink personal software	Carelink personal software integrates with Paradigm pump download	DexCom DM, consumer data manager DM 2, professional data manager	Freestyle CoPilot software

CGM is an excellent tool for patients with diabetes who are motivated and who want to optimize their control. It gives peace of mind to parents of young patients who have frequent episodes of hypoglycemia or have hypoglycemia unawareness. More experience is needed to establish its efficacy in improving diabetes control. Its use is limited to centers that have trained personnel who can teach patients to use it.

NEWER INSULIN DELIVERY SYSTEMS

Insulin delivery is now most commonly performed using insulin pens and pumps. More and more children and their families are opting for use of these alternate methods of insulin delivery over conventional insulin syringes. Pens and pumps free the patient from the need to carry and store the paraphernalia needed for traditional modes of insulin injection.

Insulin Pens

There are both pre-filled disposable and reusable pens with pre-filled cartridges. An advantage of insulin pens is that they do not need refrigeration and are accepted well by patients, especially teenagers, as the device truly looks like a pen; thus, the stigma of using a syringe and needle is avoided. Because of the pens' easy use, caretakers other than parents (school personnel, baby sitters) can be taught to be comfortable in dialing up the insulin dose.

Insulin Pumps (Continuous Subcutaneous Insulin Infusion [CSII])

The advent of insulin pumps has revolutionized insulin delivery. Continuous subcutaneous insulin infusion mimics physiological insulin secretion by providing basal insulin to inhibit glucose production by the liver. Mealtime boluses can be determined by a pre-programmed algorithm and delivered by manually pressing a button on the pump. Since its introduction in the 1970s, there have been many technological advances in delivery of the insulin with the pumps. The pumps currently in use are called "smart pumps," as they have programmable features that are built-in and enable the patient to tailor their insulin delivery more precisely to achieve fine tuning of blood glucose levels. Pumps have greatly facilitated diabetes management, allowing a more flexible lifestyle than was dictated by fixed insulin regimens, in which the timing and composition of meals had to coincide with peak action of insulin to avoid hypoglycemia and fluctuations in blood glucose levels. This single modality has made living with diabetes easier.

Technology. All pumps have an insertion set, in which a plastic cannula is inserted into

the subcutaneous (SQ) tissue using a needle guide. In general, the cannula is connected to the pump by flexible tubing. The sole exception is the Omnipod pump, in which no tubing is needed, as the catheter is part of the Omnipod itself and inserts directly into the SQ tissue. All pumps share many basic features, with some minor differences:

- Compact and easy to wear
- Programmable dosing calculators for carbohydrates and for correction of high BG
- Alarm settings for battery life and insulin volume
- Child safety locks
- Many types of boluses to suit the meal content
- 24-hour technical support
- Bolus history tracking

Additional features of the newer smart pumps include:

- Automatic communication with the BG meter
- Bolus onboard feature to avoid stacking (cumulative effect) of insulin
- Food data information and capability to add new foods
- Waterproof feature
- Variable basal patterns
- Communication with CGM
- Software for downloading all information

Commercially available insulin pumps are shown in Table 2.

Advantages of using CSII. Rapid acting insulin analogues are more physiological and more effective in controlling meal-related hyperglycemia than are older insulins.[10] Rapid acting insulin can be given using multiple doses of insulin (MDI) per day to cover meals. This at times may create problems with acceptance and adherence. One of the main barriers to optimal diabetes control in teens has been the unwillingness to give insulin injections every time they eat.

CSII provides the freedom and flexibility of lifestyle and produces better coping and acceptance of the rigors of daily diabetes care, with improved quality of life and greater adherence to recommendations.[11] Freedom from restrictions of timing and number of meals is an important issue among teenagers. Use of insulin pumps eliminates that restriction and provides greater satisfaction with diabetes management.[12] As glucose variability is lessened with basal rate adjustments, the fear of hypoglycemia diminishes, and may even be eliminated.

Metabolic advantages. CSII not only provides improvement in patient satisfaction and better acceptance of diabetes, but offers better glycemic control. Reduction of serious hypoglycemia associated with seizures and coma is significant, from 37% to 24% (Figure 1). CSII also has improved meal-related hyperglycemia and decreased the frequency of post-prandial hyperglycemia. Because HgbA1C is the standard measure of diabetes control, the effect of CSII on HgbA1C has been studied extensively. Improvement of HbgA1C has been shown in studies comparing MDI with CSII. At baseline (Figure 2) the levels were not significantly different. At 16 weeks, the CSII (pump) group had significantly lower levels compared to baseline.

Glucose variability and CSII. Glucose variability has been receiving more attention as an important indicator of metabolic control. Great variability in BG causes oxidative damage to the endothelium, and hence, leads to long-term morbidity. This effect is considered to be as damaging as exposure to hyperglycemia.[13] With CSII, insulin delivery can be adjusted to decrease or even to eliminate this variability. To reduce the degree or frequency of blood glucose variability further, it is now possible to incorporate the data from some CGM devices into the pump's memory, with the goal of having the pump adjust the settings based on the BG numbers and trends. This adjustment is done by the use of algorithms. One such algorithm was developed by the DirecNet study group.[14] DATA (*D*irecNet *A*pplied *T*reatment *A*lgorithm) provides guidelines that help the CSII/CGM

Table 2. Comparative Features of Insulin Pump Varieties

Features	Animas IR2020	Medtronic Paradigm	Accu-Chek Spirit	Insulet Omnipod	Sooil/USA diabecareIIS
Battery life	6 wks to 8 wks	3 wks	3 wks	4 wks	8 to 10 wks
Reservoir size	200 units	300 units	176 or 300 units	200 units	300 units
Basal increment	0.025 U	0.05 U	0.05 U	0.05 U	0.01 to 0.1 U
Bolus increment	0.05 U	0.05 U	0.1 U	0.05 U	0.1 U
Carbohydrate and correction dosing	Manual /Bolus Calculator	Manual /Bolus Wizard	Manual /Bolus Calculator	Bolus Calculator	Manual /Bolus Calculator
BG meter link	Manual entry Link with Ultra Ping	Manual entry Link with Ultra	Link with Ultra		

Figure 1. Frequency of Hypoglycemia (Low Blood Glucose) Events

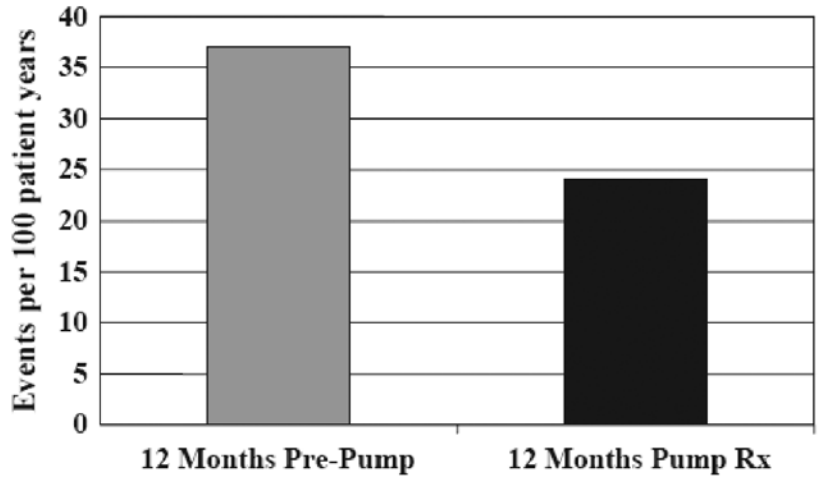
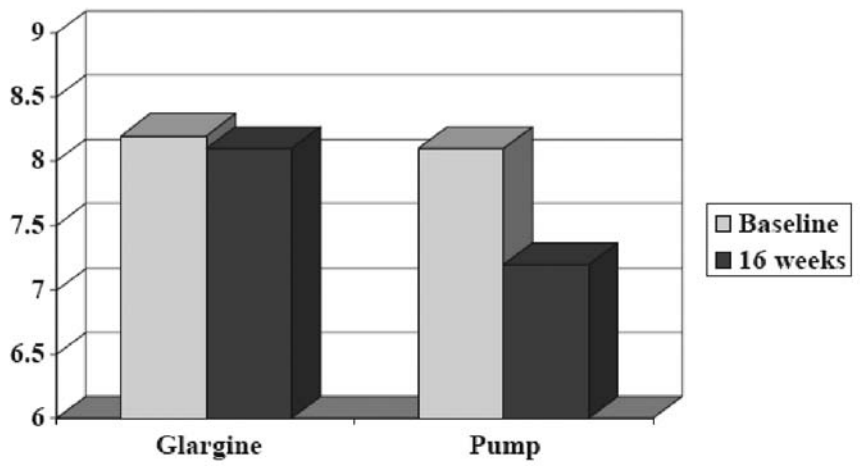


Figure 2. Changes in HbA1c in Yale Randomized Clinical Trial Comparing MDI with Glargine and CSII



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user to modulate the pump settings for more accurate insulin dosing and to reduce blood glucose variability.

CLOSED LOOP SYSTEM (ARTIFICIAL PANCREAS)

With technological advances, combining of CGM and the newer programmable external pumps, along with a built-in algorithm that automatically adjusts the insulin delivery based on BG readings from the sensor, constitutes the "closed loop" or "artificial pancreas."[15] This insulin delivery system more closely reproduces normal beta cell function in achieving near normal glycemia. However, as the glucose readings obtained from CGM lag behind blood glucose concentrations, and subcutaneous insulin delivery lags behind the physiologic portal delivery route, the ability of the closed loop system to lower post-prandial hyperglycemia is not yet ideal. However, it is superior to other currently available alternatives. The future of this concept of closed loop artificial pancreas is being explored further under the JDRF Artificial Pancreas Project.

SUMMARY

The discovery of insulin dramatically changed management of diabetes. Since then many new modalities have improved both short-term and long-term diabetes care. Newer technological strategies and tools have not only made living with diabetes easier, but have improved metabolic outcomes. In the future, further refinement of glucose monitoring and insulin delivery systems will pave the way for improved access of the latest technologies to all patients with diabetes, the ultimately leading to development of a true artificial pancreas.

REFERENCES

1. The Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med.* 1993;329:977–986.

2. Hönes J, Müller P, Surridge N. The technology behind glucose meters: test strips. *Diabetes Technol Ther.* 2008;10(Suppl.1):S10-S26.

3. Subramanian SL, Hirsch IB. The utility and recent advances in self-monitoring of blood glucose in type 1 diabetes. *Diabetes Technol Ther.* 2008,;10(Suppl. 1):S43-S50.

4. Bui H, Perlman K, Daneman D. Self-monitoring of blood glucose in children and teens with diabetes. *Pediatr Diabetes*. 2005;6:50–62.

5. Bina DM, Anderson RL, Johnson ML, et al. Clinical impact of prandial state, exercise, and site preparation on the equivalence of alternative-site blood glucose testing. *Diabetes Care*. 2003;26:981–985.

6. Boyne MS, Silver DM, Kaplan J, et al. Timing of changes in interstitial and venous blood glucose measured with a continuous subcutaneous glucose sensor. *Diabetes.* 2003;52:2790-2794.

7. Deiss D, Bolinder J, Riveline JP, et al. Improved glycemic control in poorly controlled patients with type 1 diabetes using real-time

continuous glucose monitoring. *Diabetes Care.* 2006;29:2730-2732.

8. Garg S, Zisser H, Schwartz S, et al. Improvement in glycemic excursions with a transcutaneous, real-time continuous glucose sensor: a randomized controlled trial. *Diabetes Care.* 2006;29:44-50.

9. Buckingham B, DirecNet. Continuous glucose monitoring in children with type 1 diabetes. *J Pediatr*. 2007;151:388-393.

10. Howey DC, Bowsher RR, Brunelle Rl, et al. {Lys (B28), Pro (B29)}- human insulin: a rapidly absorbed analogue of human insulin. *Diabetes.* 1994;43:396-402.

11. Low KG, Massa L, Lehman D, et al. Insulin pump use in young adolescents with type 1 diabetes: a descriptive study. *Pediatr Diabetes.* 2005;6(1):22-31.

12. Weintrob N, Benzaquen H, Galatzer A, et al. Comparison of continuous subcutaneous insulin infusion and multiple daily injection regimens in children with type 1 diabetes: a randomized open crossover trial. *Pediatrics.* 2003;112(3 Pt. 1):559-564.

13. Hirsch, IB. Intensifying insulin therapy in patients with type 2 diabetes mellitus. *Am J Med.* 2005;118(Suppl. 5A):S21-S26.

14. Diabetes Research in Children Network (DirecNet) Study Group. Use of the DirecNet applied treatment algorithm (DATA) for diabetes management with a real-time continuous glucose monitor (the Freestyle Navigator). *Pediatr Diabetes*. 2008;9(2):12-47.

15. Weinzimer SA, Steil GM, Swan KL, et al. Fully automated closed loop insulin delivery versus semiautomated hybrid control in pediatric patients with type 1 diabetes using an artificial pancreas.*Diabetes Care*. 2008;31:5,934-939.