Diabetes Devices

Michael J. Fowler, MD

Editor's note: This article is the 7th in a 12-part series reviewing the fundamentals of diabetes care for physicians in training. Previous articles in the series can be viewed at the Clinical Diabetes *website (http://clinical.diabetesjournals.org).*

Nowhere in the medical world is progress more evident than in the treatment of diabetes. Less than a century ago, diabetes was virtually uncontrollable and, especially in the case of type 1 diabetes, could be considered a terminal disease. The discovery and use of insulin in the 1920s allowed individuals to control diabetes to an extent, but commercial blood glucose testing techniques would not become available for 50 more years. Patients' daily routine was centered on treating the disease, which included boiling syringes and sharpening needles, injecting animal-based insulin formulations, maintaining unvarying diets and daily activity, and dealing with seemingly unpredictable fluctuations in blood glucose levels. Patients' lives revolved around the treatment of a disease over which they had very limited control.

During recent decades, however, treatment of diabetes has changed profoundly. The ability to control blood glucose levels has improved tremendously, and the time required to do so has decreased. The improvements are particularly evident in regard to instruments used to monitor glucose and to administer insulin.

Insulin Pens

The goal of insulin administration is to normalize blood glucose levels, whether a patient has type 1 or type 2 diabetes. Normalization of glucose levels decreases patients' risk of developing microvascular complications in type 1 or type 2 diabetes and has also been shown to decrease the risk of developing macrovascular complications in type 1 diabetes.[1–3]

Historically, insulin has been administered via a syringe that is filled from a vial of insulin. More recently, refillable pen-like injection devices and prefilled disposable pens have become available as alternatives. Still more recently, insulin administration options have expanded to include inhaled products and formulations that are forced subcutaneously via a burst of air, but these techniques are used less frequently, and there is currently no commercially available inhaled insulin product. Insulin pens are frequently used by patients to administer both long-acting and short-acting insulin in either basal-only, split-mixed (usually involving two daily injections of long- and short-acting insulin mixtures), or basal-bolus insulin regimens.

In administering insulin, both accuracy and precision are crucial. Excessive insulin delivery predisposes patients to hypoglycemia and weight gain, both of which can have dire consequences. Inadequate insulin delivery predisposes to hyperglycemia, which increases the risk of complications. Lack of precision in insulin measurement (i.e., variability in insulin administration from dose to dose) can lead to increased fluctuation in glucose levels. Both the short- and long-term health and safety of patients, therefore, depends on accurate and precise insulin dosing and administration. This is especially important in populations of patients who may have increased difficulty in self-administering insulin, such as pediatric and elderly patients.

Most short-acting and long-acting insulin products are now available in pen injector devices. These are available as either prefilled, disposable pens or as refillable pens, which deliver insulin from replaceable cartridges. Most are specially designed so that patients with diminished eyesight or tremors can still use them, and some are especially designed to make administration easier for people with limited dexterity or vision.

Studies in children have demonstrated that insulin pens may be more accurate than syringes for measuring insulin at low doses. Lteif and Schwenk studied children measuring their own doses of insulin and administering the insulin into a vial. Insulin syringe measurement of insulin was significantly less accurate than pens when measuring small (< 5-unit) doses of insulin. Reproducibility of insulin dosing was better with larger doses of insulin but not significantly different between insulin pens and syringes.[4] Other studies have shown that elderly patients may be more capable of self-administering insulin using insulin pens compared to using vial and syringes.[5] This is an important factor when considering the aging United States population, as well as increasingly early discharges from hospital

stays during which elderly patients may have been taught to use insulin for the first time.

When using similar insulin treatment regimens, the majority of patients may prefer insulin pens to vials and syringes. One study of 121 subjects suggested that patients consider insulin pens to be more discreet when they need to administer insulin in public places and found insulin pens easier to use than syringes overall. However, the same study did not show improvements in overall glycemic control in patients using pens compared to those using vials and syringes. Safety profiles in patients were similar.[6] Patients' adherence to their insulin regimen may be improved with insulin pen use, as well.[7] Additionally, patients' decisions to try insulin pens may depend heavily on the recommendation of their treating physician.[8]

The major disadvantage of using insulin pens, like other new diabetes technology, is cost. Insulin analogs are ~ 30% more expensive per unit when purchased as prefilled or refillable pens than when purchased in vials. As a result, insurance companies may be reluctant to cover the additional cost of insulin administration from pen devices unless there are extenuating factors, such as tremor or diminished eyesight.

Monitoring Glucose

With the exception of the discovery of insulin, the development of self-monitoring of blood glucose (SMBG) may be the most important advance in diabetes management. Before the commercial availability of blood glucose meters, patients monitored their response to therapy by estimating the glucose concentration in urine. Essentially, patients relied on an inaccurate estimation of glucose control to adjust medications such as insulin doses. SMBG has allowed patients much more accurate measurement of glycemic control, which in turn allows more intelligent titration of medication.

Glucose monitoring has been proven to be effective in patients with type 1 diabetes.[9] Performed at least daily in pharmacologically treated patients with type 2 diabetes, it has been associated with improved glycemic control.[10] Although some studies have shown improved glycemic control in patients performing SMBG, all studies have not reached such conclusions.[9,11,12] The American Diabetes Association (ADA) recommends that SMBG be performed three or more times daily for patients who are using multiple daily doses of insulin or insulin pump therapy. For patients who are on other regimens, such as oral agents, or basal insulin therapy, SMBG may still be useful in achieving adequate glycemic control, especially postprandially.[13]

Glucose meters have changed considerably in the 20 years since their arrival. The time required to analyze a sample has dropped from minutes to just a few seconds. The quantity of blood required for analysis has declined to around 1/100 of that originally necessary, with some meters requiring as little as a fraction of a microliter of blood. As a result, many meters allow the operator to perform testing at alternate sites, such as the palm or forearm. The meters have also become easier to operate and smaller and have larger and easier-to-read displays. Early glucose meters used reflectance (optical) technology to estimate glucose levels, but most new meters (still not all) use glucose oxidase to estimate glucose levels via electrochemical signaling.

The ADA's stated goal for meter accuracy is that 100% of readings from a particular meter should be within 5% of reference methods, such as a laboratory glucose analyzer. Handheld meters commonly do not meet such stringent criteria, however. It is important to remember that the accuracy of a glucose meter is dependent on many variables. Because most meters use an enzymatic method of glucose measurement, results can be affected by temperature and altitude (oxygen concentration). Other factors that affect accuracy include hematocrit, adequacy of peripheral circulation, and the presence of glucose on the skin surface at the time of testing. It is beyond the scope of this article to review such parameters for all commercially available meters, but it is advisable that physicians be familiar with such parameters in meters they customarily prescribe.[14–16]

Continuous glucose monitoring (CGM) devices have been commercially available for more than a year and are being increasingly used by patients. These devices consist of a subcutaneous monitor that measures the glucose concentration of interstitial fluid (usually a close approximation of blood glucose concentration). They are not, however, accurate enough to obviate the need for SMBG because they tend to be less accurate than direct glucose measurements, especially during times of rapid glucose fluctuation.

CGM has not yet been definitively shown to improve overall metabolic glucose control and decrease the risk of complications, but studies have suggested that they are helpful in decreasing glucose excursions and stabilizing glucose levels.[17] They may also be particularly useful in providing early warning alarms for hypoglycemia in patients suffering from hypoglycemia unawareness.[18] The ADA has addressed CGM in its 2008 Standards of Care. The guidelines state that CGM may be useful in the treatment of type 1 diabetes but does not replace the need for peripheral blood draw and use of a handheld glucose meter.[13]

One major disadvantage of CGM is its price. If not covered by insurance, the initial patient expenditure for the devices can range from $400 to >$2,000. The cost of the devices'

disposable sensors, which must be changed every 3–7 days, can add several hundred dollars per month, in addition to the cost for SMBG supplies necessary for frequent calibrations of the CGM systems. Initial and ongoing costs are currently a major obstacle in obtaining insurance company approval for such monitoring.

Insulin Pumps

Insulin pumps have been commercially available since the 1970s to control glucose levels in patients primarily with type 1 diabetes. Rather than receiving multiple daily subcutaneous injections of short- and either long- or intermediate-acting insulin, patients using an insulin pump receive a continuous subcutaneous infusion of short-acting insulin. These devices hold an insulin reservoir and supply insulin via a plastic tube into subcutaneous tissue. The tube is changed periodically, usually every 3 days. Several pumps are available and vary in both size and price.

Insulin pump therapy offers several advantages over multiple daily injection therapy. Pumps are able to more precisely dose insulin compared to insulin syringes or pens. Some pumps currently available are capable of administering insulin to 1⁄20 of a unit. Precise insulin doses can be helpful in the treatment of patients who are very insulin sensitive, such as those with type 1 diabetes. Pumps are also programmable to provide different doses of basal insulin throughout the day. This feature allows patients to increase their basal insulin, for example, to counteract the "dawn phenomenon" or to decrease their basal rate to compensate for increased physical activity.

Insulin pumps in some, but not all, studies have been associated with improved metabolic control and lower risk of mild and severe hypoglycemia in patients with type 1 diabetes.[19,20] Most studies also show that the A1C improvement is modest, usually less than one percentage point. Some of the newest insulin pumps are also available with integrated continuous glucose monitoring devices.

Insulin pumps do require considerable dedication on the part of both patients and caregivers. Pumps can malfunction and require replacement, which forces a patient to rapidly resume insulin injections pending arrival of a new pump. Patients can experience catheter occlusions that interrupt the flow of insulin. For this reason, patients must be especially cognizant of their glucose level and prepared to change their insulin infusion set to address recurrent unexplained hyperglycemia. Because insulin pumps can be labor-intensive and technically challenging, careful patient selection is one of the most important elements in successful pump therapy.

Diabetes care, as much or more than other areas of medical care, has advanced profoundly during the past 80 years. Patients are now able to use devices with advanced technology that assist them in controlling glucose levels. These devices are a major reason that diabetes may be controlled much more effectively now than in the past. Although many of these devices are quite expensive, they are becoming increasingly commonplace. No single glucose meter, CGM system, insulin pen, or pump is right for everyone; approaches to controlling glucose levels must be individually tailored to each patient's needs. It is important for physicians to be familiar with the characteristics of these devices to help patients decide which ones will most help them manage their glucose levels.

REFERENCES

[1]DCCT 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* 329:977–986, 1993

[2]U.K. Prospective Diabetes Study Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352:837–853, 1998

[3]Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, Raskin P, Zinman B: Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 353:2643–2653, 2005

[4]Lteif AN, Schwenk WF: Accuracy of pen injectors versus insulin syringes in children with type 1 diabetes. *Diabetes Care* 22:137–140, 1999

[5]Shelmet J, Schwartz S, Cappleman J, Peterson G, Skovlund S, Lytzen L, Nicklasson L, Liang J, Lyness W: Preference and resource utilization in elderly patients: InnoLet versus vial/syringe. *Diabetes Res Clin Pract* 63:27–35, 2004

[6]Korytkowski M, Bell D, Jacobsen C, Suwannasari R: A multicenter, randomized, open-label, comparative, two-period crossover trial of preference, efficacy, and safety profiles of a prefilled, disposable pen and conventional vial/syringe for insulin injection in patients with type 1 or 2 diabetes mellitus. *Clin Ther* 25:2836–2848, 2003

[7]Lee WC, Balu S, Cobden D, Joshi AV, Pashos CL: Medication adherence and the associated health-economic impact among patients with type 2 diabetes mellitus converting to insulin pen therapy: an analysis of third-party managed care claims data. *Clin Ther* 28:1712–1725; discussion 1710–1711, 2006

[8]Rubin RR, Peyrot M: Factors affecting use of insulin pens by patients with type 2 diabetes. *Diabetes Care* 31:430–432, 2008

[9]Welschen LM, Bloemendal E, Nijpels G, Dekker JM, Heine RJ, Stalman WA, Bouter LM: Self-monitoring of blood glucose in patients with type 2 diabetes who are not using insulin: a systematic review. *Diabetes Care* 28:1510–1517, 2005

[10]Karter AJ, Ackerson LM, Darbinian JA, D'Agostino RB, Jr., Ferrara A, Liu J, Selby JV: Self-monitoring of blood glucose levels and glycemic control: the Northern California Kaiser Permanente Diabetes registry. *Am J Med* 111:1–9, 2001

[11]Davis WA, Bruce DG, Davis TM: Does self-monitoring of blood glucose improve outcome in type 2 diabetes? The Fremantle Diabetes Study. *Diabetologia* 50:510–515, 2007

[12]Guerci B, Drouin P, Grange V, Bougneres P, Fontaine P, Kerlan V, Passa P, Thivolet C, Vialettes B, Charbonnel B: Self-monitoring of blood glucose significantly improves metabolic control in patients with type 2 diabetes mellitus: the Auto-Surveillance Intervention Active (ASIA) study. *Diabetes Metab* 29:587–594, 2003

[13]American Diabetes Association: Standards of medical care in diabetes—2008 [Position Statement]. *Diabetes Care* 31 (Suppl. 1):S12–54, 2008

[14]Weitgasser R, Hofmann M, Gappmayer B, Garstenauer C: New, small, fast-acting blood glucose meters—an analytical laboratory evaluation. *Swiss Med Wkly* 137:536–540, 2007

[15]Fink KS, Christensen DB, Ellsworth A: Effect of high altitude on blood glucose meter performance. *Diabetes Technol Ther* 4:627–635, 2002

[16]Thomas LE, Kane MP, Bakst G, Busch RS, Hamilton RA, Abelseth JM: A glucose meter accuracy and precision comparison: the FreeStyle Flash versus the Accu-Chek Advantage, Accu-Chek Compact Plus, Ascensia Contour, and the BD Logic. *Diabetes Technol Ther* 10:102–110, 2008

[17]Garg S, Zisser H, Schwartz S, Bailey T, Kaplan R, Ellis S, Jovanovic L: Improvement in glycemic excursions with a transcutaneous, real-time continuous glucose sensor: a randomized controlled trial. *Diabetes Care* 29:44-50, 2006

[18]Chico A, Vidal-Rios P, Subira M, Novials A: The continuous glucose monitoring system is useful for detecting unrecognized hypoglycemias in patients with type 1 and type 2 diabetes but is not better than frequent capillary glucose measurements for improving metabolic control. *Diabetes Care* 26:1153–1157, 2003

[19]Weissberg-Benchell J, Antisdel-Lomaglio J, Seshadri R: Insulin pump therapy: a meta-analysis. *Diabetes Care* 26:1079–1087, 2003

[20]Retnakaran R, Hochman J, DeVries JH, Hanaire-Broutin H, Heine RJ, Melki V, Zinman B: Continuous subcutaneous insulin infusion versus multiple daily injections: the impact of baseline A1c. *Diabetes Care* 27:2590–2596, 2004

Michael J. Fowler, MD, is an assistant professor of medicine in the Division of Diabetes, Endocrinology, and Metabolism, Vanderbilt Eskind Diabetes Clinic, at Vanderbilt University Medical Center in Nashville, Tenn. He is an associate editor of Clinical Diabetes.

Note of disclosure: *Dr. Fowler has received honoraria for speaking engagements and grant support from Novo Nordisk, which manufactures insulin pen devices.*