BEST PRACTICES IN: Preventing Hypoglycemia by Continuous Glucose Monitoring

Since the results of the Diabetes Control and Complications Trial (DCCT) were reported in 1993, clinicians have known that tight glucose control reduces the risk of diabetic complications in patients with type 1 diabetes.[1] Several years later, the long-term extension of the DCCT study, called the Epidemiology of Diabetes Interventions and Complications (EDIC) study, extended the benefits of early tight glycemic control to reducing the risk of cardiovascular complications, which account for two thirds to three fourths of mortality in patients with diabetes.[2,3]

A recent update of the DCCT/EDIC data, reflecting 30 years of follow-up, showed that the benefits of early tight glycemic control are long-lasting "legacy" effects.[4] During the intitial phases of the DCCT study, the difference in mean glycosylated hemoglobin A1C (HbA_{1c}) values for the two groups was approximately 2% (~7 vs 9%); however, during the extension phase of the EDIC, the mean A1C values for both groups merged to approximately 8% and were not different statistically. In conventionally managed patients in the DCCT cohort, the incidences of proliferative retinopathy, nephropathy, and cardiovascular disease were 50%, 25%, and 14%, respectively. Corresponding values in the EDIC cohort were 47%, 17%, and 14%. In contrast, patients assigned to tight control had a 21% incidence of proliferative retinopathy, 9% incidence of nephropathy, and 9% incidence of cardiovascular disease. Early tight control had long-lasting effects even though the control was not nearly as tight for the duration of the EDIC protocol. The phenomenon has been termed metabolic memory and highlights the benefits of intensively controlling glucose levels from the time of diagnosis.

The impact of the DCCT and EDIC data on diabetes care cannot be overestimated; however, the trial data had a downside that received considerably less attention. Intense glucose control increased the frequency of severe hypoglycemia by as much as threefold.[1]

Hypoglycemia remains the principal complication of tight glycemic control and poses the principal obstacle to effective and consistent intensive glucose control in diabetes. Data from the DCCT showed that 70% of patients who wanted to improve glycemic control feared hypoglycemia and considered it a major barrier to more intense management.[5] Fear of hypoglycemia and associated reluctance to strive for tight control can lead to poor control and unacceptably high glucose values.

Frequent episodes of hypoglycemia can disrupt the body's counterregulatory mechanisms and blunt normal responses to subsequent hypoglycemia in intensively treated patients with diabetes. The end result is a phenomenon known as "hypoglycemia unawareness," which leads to a vicious cycle of recurrent hypoglycemia.[6]

The potential consequences of hypoglycemia should not be underestimated. Hypoglycemia poses a risk not only for the patient with diabetes but potentially others who come in contact with the patient. We recently reviewed three cases involving patients with diabetes who had hypoglycemic episodes while driving, resulting in accidents that caused one or more fatalities. In the DCCT, 1.5% of severe hypoglycemia incidents were associated with automobile accidents.[7] The so-called "dead-in-bed" syndrome (unexplained deaths presumably caused by hypoglycemia) is thought to be responsible for 6% of deaths among patients with type 1 diabetes younger than 40.[8-10]

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Home Glucose Monitoring

Over the past 25 to 30 years, technology for home glucose monitoring has improved continually, particularly finger-stick technology. However, the fact remains that home monitoring provides a static representation of glucose levels, which are anything but static in a patient with diabetes. A patient who performs finger-stick testing four to eight times a day learns about blood glucose status for little more than eight of the 1,440 minutes in a day.

Patients who fear hypoglycemia may develop near-obsessive behavior regarding glucose monitoring and perform finger-stick measurements almost hourly. Regardless of the frequency of finger-stick monitoring, the fact remains that one is getting information at one point in time with no idea of the trend or direction of glucose values.

Self-monitoring of blood glucose (SMBG) by conventional techniques cannot tell a patient whether blood glucose is declining from an already low level, is decreasing from a high level in response to an insulin bolus, or has been stable for the past hour. With finger-stick monitoring, patients have no way of knowing the current or recent direction of blood glucose levels. A patient may not become aware of a falling glucose level until symptoms of hypoglycemia arise. Some patients with hypoglycemia unawareness have no warning symptoms.[7] Conversely, a patient's blood glucose level might soar to 300 mg/dL or 400 mg/dL without producing any acute symptoms.[11]

Classically, the major influences on blood glucose levels have been diet, exercise, and insulin dose.[7] However, a single-minded focus on those three factors excludes a host of other variables that have a major impact on glucose levels: the nutritional makeup of a meal,[12] timing of insulin doses,[13] menstrual periods,[14] digestion,[15] time of the day,[16] seasonal differences,[17] stress,[18] and other hormonal and environmental factors, to name just a few.

Continuous Glucose Monitoring

Continuous glucose monitoring (CGM) provides primarily patients and secondarily physicians with the information that has been missing in therapeutic strategies designed to achieve tight glucose control in the safest manner possible. CGM devices measure glucose over time and produce a new reading every 1 to 5 minutes. As a result, patients become aware of swings in blood glucose levels much sooner and can respond promptly to prevent episodes of hypoglycemia or to bring down rising glucose levels before they become dangerously elevated.

Because CGM devices have the ability to set "glucose thresholds" that trigger vibratory and audible alarms, CGM addresses the fear of hypoglycemia that many patients with diabetes have and offers a way to guard against having a serious low, especially in those with hypoglycemia unawareness. In one representative randomized trial, investigators examined the impact of CGM in 91 patients with type 1 diabetes.[19] Use of CGM was associated with a 21% reduction in the time spent in hypoglycemia (≤55 mg/dL), 23% less time in hyperglycemia (≥240 mg/dL), and a 24% increase in the time spent within the target range for blood glucose (81 mg/dL to 140 mg/dL).

In most instances, patients have little or no difficulty learning how to use the CGM devices. They usually find that the devices do not cause unacceptable intrusions into daily activities.[20]

Patients with diabetes who have "special circumstances"—such as patients with hypoglycemia unawareness and patients who are pregnant[21]—have clearly been shown to benefit from CGM. Other groups, such as patients with gastroparesis and those with type 2 diabetes on insulin regimens, may also stand to benefit from CGM, although further studies in this area are needed.

Even patients with well-controlled diabetes can benefit from CGM, as shown in a large randomized clinical trial that compared CGM to SMBG in children and adults with type 1 diabetes.[22] A subset of the patients had baseline HbA_{1c} values <7%. After 26 weeks of follow-up, patients assigned to CGM had spent significantly less time with glucose levels of 60 mg/dL or lower (P=0.05), significantly less time outside the target blood glucose range of ≤70 mg/dL to >180 mg/dL (P=0.003), and had a significantly lower mean HbA_{1c}, (6.4% at baseline and 26 weeks vs 6.5% and 6.8% in the control group, P<0.001). However, the groups did not differ with respect to the frequency of severe hypoglycemia.

As research has proven the value of CGM, and the adoption of the technology has evolved, the American Diabetes Association has revised its clinical practice recommendations to address CGM more specifically than in the past.[23] The 2009 recommendations state that CGM can be useful in conjunction with intensive insulin therapy to lower HbA_{1c} levels in adults with type 1 diabetes, may be useful in the management of children and teenagers with type 1 diabetes, and may be useful for patients who have frequent episodes of hypoglycemia or who have hypoglycemia unawareness.

Clinicians can offer patients more than one option for CGM. Currently, three manufacturers have four FDA-approved CGM monitors. All of the available devices have demonstrated the ability to obtain reasonably accurate blood glucose measurements on a consistent basis in comparison to conventional SMBG or YSI laboratory venous glucose values.[19,24,25] The situation in which CGM devices have shown the least accuracy is during times of either rapidly rising or rapidly decreasing blood glucose. During these times, the glucose reading on the CGM device may lag compared to venous glucose sampling results.[24] However, the lag times demonstrated will vary depending in part on the type of CGM, and the discrepancies can be minimized by appropriate selection of a CGM device.[26] For this reason, incorporating the information given by trend arrows on CGM devices may be necessary rather than just relying on the most recent glucose value displayed.

CGM devices are not worry free for every patient. Skin reactions have been reported at insertion sites, some rarely classified as "severe" by investigators.[20] Some patients develop "sensor burnout" if the software that drives the devices develops problems that lead to poor calibration of the device or values that differ from those obtained with SMBG. Frequent alarms pose problems for some patients but often can be mitigated by learning how to better troubleshoot their device, properly setting the alarm thresholds, or choosing a different CGM device. Like all advances in technology, some patients are resistant or do not benefit from CGM for a host of different physical, financial, and emotional barriers. However, most patients incorporate the devices into diabetes management and daily living with little or no difficulty.[20]

The reimbursement climate for CGM continues to improve. Most commercial insurers cover CGM devices for patients with type 1 diabetes who meet specific criteria; some payors cover for patients with type 2 diabetes requiring insulin therapy. The clinically proven ability of CGM to reduce hypoglycemia-associated complications, costs, and adverse effects on glucose control has played a major role in shaping the reimbursement environment.

Summary

Tight glucose control remains the standard of care for patients with type 1 diabetes and patients with type 2 diabetes requiring insulin therapy. However, hypoglycemia and the fear of hypoglycemia pose the major obstacles to effective implementation of regimens designed to achieve adequate glycemic control. Conventional SMBG fails to address those obstacles by providing only static information from glucose assessments at a few specific times each day. SMBG provides patients and physicians with limited information about the bigger picture of blood glucose levels throughout the day and night, namely, the trends and directions of glucose values over time. As a consequence, conventional SMBG may actually contribute to problems and concerns related to hypoglycemia in certain situations.

A large volume of scientific and clinical evidence shows that CGM addresses the key issues of tight control: maintaining blood glucose levels within the target range while avoiding hypoglycemia. As a person with type 1 diabetes since 1970, as well as a diabetologist, I bring a different perspective to the clinical setting, compared with most other clinicians who care for patients with diabetes. Having used CGM for several years, I could never return to conventional methods of self-monitoring. By reducing the frequency and duration of hypoglycemia and hyperglycemia, CGM makes living with diabetes easier and safer and improves the quality of life for patients with diabetes that requires insulin therapy.

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. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. *N Engl J Med*. 2000;342:381-389.
3. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Sustained effect of intensive treatment of type 1 diabetes mellitus on development and progression of diabetic nephropathy: The Epidemiology of Diabetes Interventions and Complications (EDIC) study. *JAMA*. 2003;290:2159-2167.
4. Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group. Modern-day clinical course of type 1 diabetes mellitus after 30 years' duration. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications and Pittsburgh Epidemiology of Diabetes Complications experience (1983-2005). *Arch Intern Med*. 2009;169:1307-1316.
5. Thompson CJ, Cummings JF, Chalmers J, Gould C. Newton RW. How have patients reacted to the implications of the DCCT? *Diabetes Care*. 1996;19:876-879.
6. Davis SN, Mann S, Briscoe VJ, Ertl AC, Tate DB. Effects of intensive therapy and antecedent hypoglycemia on counterregulatory responses to hypoglycemia in type 2 diabetes. *Diabetes*. 2009;58:701-709.
7. The Diabetes Control and Complications Trial Research Group. Epidemiology of severe hypoglycemia in the Diabetes Control and Complications Trial. *Am J Med*. 1991;90:450-459.
8. Tattersall RB, Gill GV. Unexplained deaths of type 1 diabetic patients. *Diabet Med*. 1991;8:49-58.
9. Søvik O, Thordarson H. Dead in bed syndrome in young diabetic patients. *Diabetes Care*. 1999;22(Suppl 2):B40-B42. Erratum in: *Diabetes Care*. 1999;22:1389.
10. Thordarson H, Søvik O. Dead in bed syndrome in young diabetic patients in Norway. *Diabet Med*. 1995;12:782-787.
11. Bonakdaran S, Rajabian R. Prevalence and extent of glycemic excursions in well-controlled patients with type 2 diabetes mellitus using continuous glucose-monitoring system. *Indian J Med Sci*. 2009;63:66-71.
12. Pearce KL, Noakes M, Keogh J, Clifton PM. Effect of carbohydrate distribution on postprandial glucose peaks with the use of continuous glucose monitoring in type 2 diabetes. *Am J Clin Nutr*. 2008;87:638-644.
13. Jovanovic L, Giammattei J, Acquistapace M, et al. Efficacy comparison between preprandial and postprandial insulin aspart administration with dose adjustment for unpredictable meal size. *Clin Ther*. 2004;26:1492-1497.
14. Valdes CT, Elkind-Hirsch KE. Intravenous glucose tolerance test-derived insulin sensitivity changes during the menstrual cycle. *J Clin Endocrinol Metab*. 1991;72:642-646.
15. Ishii M, Nakamura T, Kasai F, Onuma T, Baba T, Takebe K. Altered postprandial insulin requirement in IDDM patients with gastroparesis. *Diabetes Care*. 1994;19:901–903.
16. Carroll M, Schade DS. The dawn phenomenon revisited: Implications for diabetes therapy. *Endocr Pract*. 2005;11:55-64.
17. Bunout D, Barrera G, de la Maza P, Gattas V, Hirsch S. Seasonal variation in insulin sensitivity in healthy elderly people. *Nutrition*. 2003;19:310-316.
18. Nonogaki K, Iguchi A. Stress, acute hyperglycemia, and hyperlipidemia role of the autonomic nervous system and cytokines. *Trends Endocrinol Metab*. 1997;8:192-197.
19. 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.
20. The Diabetes Research in Children Network (DirecNet) Study Group. Continuous glucose monitoring in children with type 1 diabetes. *J Pediatr*. 2007;151:388-93, 393.e1-2. Epub 2007 Aug 24.
21. Murphy HR, Rayman G, Lewis K, et al. Effectiveness of continuous glucose monitoring in pregnant women with diabetes: Randomised clinical trial. *BMJ*. 2008 Sep 25;337:a1680. doi: 10.1136/bmj.a1680.
22. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. The effect of continuous glucose monitoring in well-controlled type 1 diabetes. *Diabetes Care*. 2009;32:1378-1383.
23. American Diabetes Association. Standards of medical care in diabetes—2009. *Diabetes Care*. 2009;32(suppl 1):S13-S61.
24. Weinstein RL, Schwartz SL, Brazg RL, Bugler JR, Peyser TA, McGarraugh GV. Accuracy of the 5-day FreeStyle Navigator Continuous Glucose Monitoring System: Comparison with frequent laboratory reference measurements. *Diabetes Care*. 2007;30:1125-1130. Epub 2007 Mar 2.
25. The Diabetes Research in Children Network (DirecNet) Study Group. The accuracy of the Guardian® RT continuous glucose monitor in children with type 1 diabetes. *Diabetes Technol Ther*. 2008;10:266-272.
26. Kamath A, Mahalingam A, Brauker J. Analysis of time lags and other sources of error of the DexCom SEVEN continuous glucose monitoring. *Diabetes Technol Ther*. 2009;11:689-695.

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