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# Patient-centered diabetic care: the role of continuous glucose monitoring

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With more than 23.6 million Americans living with diabetes mellitus and a growing rate of 1.6 million new cases per year, improved control and the prevention of secondary complications is imperative. Reliance on hemoglobin A1c reading alone can be misleading to the physician and its value difficult for the patient to comprehend. Moreover, current research suggests that glycemic spikes, undetected by hemoglobin A1c, are a risk factor for the development of vascular and neurologic complications. Three-day continuous glucose monitoring offers a decided advantage in control of diabetes and also involves the patient in decision-making. Data collected by the monitor is downloaded into a computer and printed out, in color, as pie charts, daily line graphs, and composite summaries. Patient-recorded glucometer values are also displayed on the line graphs. The physician can review the summaries for episodes of hypoglycemia and glycemic spikes and make immediate correction to the care plan if necessary. When these summaries are presented to the patient, they can easily comprehend the effect their diet, activity, and medications have on their disease state. Furthermore, capillary sensor data is compared with patient-recorded glucometer values in an effort to evaluate technique and identify inaccurate glucometers. Enhanced understanding on the part of the patient and physician, as well as joint collaboration, has been proven to improve control of this disease.


Patient-centered care has been the hallmark of osteopathic medicine since its inception. Continuous glucose monitoring provides the osteopathic physician with the ability to approach the patient with diabetes mellitus with easily understood data and explain and review current evidenced-based guidelines of treatment and provide suggestions for control, with aim at secondary disease prevention. Treatment of this disease thus becomes a joint undertaking that has been shown to provide improved control and better patient compliance.

Family physicians on the front line of medicine are faced with a serious challenge from diabetes mellitus, a disease now affecting more than 23.6 million Americans (approximately 8% of the population) and growing by 1.6 million new cases each year.[1] Despite seemingly adequate blood glucose control, as measured by current standards, micro and macrovascular disease complications, as well as autonomic and peripheral nerve damage, continue to occur. Diabetic complications occur less frequently in closely controlled people with diabetes than in their less well-controlled counterparts. The occurrence of these complications, however, in the closely controlled subset raises an issue and suggests further investigation.

Two landmark studies have shown the importance of tight glycemic control in the prevention of diabetic complications. The Diabetes Control and Complications Trial (DCCT) compared conventional and intensive care in people with type 1 diabetes targeting an A1c of 7% in the intensive group.[2] The United Kingdom Prospective Diabetes Study (UKPDS) compared conventional and intensive

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care in newly diagnosed type 2 diabetics, targeting fasting glucose and a low A1c.[3] Both studies clearly revealed a marked reduction in diabetic complications in the intensive care group when compared with the group receiving conventional therapy. The UKPDS study, in addition, demonstrated a positive economic impact by intensively treating patients with diabetes mellitus.[4]

The Kumamoto Study also compared intensive type 2 diabetic treatment using multiple daily insulin injections with conventional treatment and concluded that intensive glycemic control delayed the onset and progression of microvascular disease. In addition, there was an improvement in nerve conduction and a significantly lower incidence of the development or progression of nephropathy in the intensely treated group. This study differed from the DCCT and UKPDS in that it also targeted postprandial glucose to <200 mg/dL and the mean amplitude of glycemic excursions (MAGE) to <100 mg/dL and used these parameters to adjust insulin dosage in the intensely treated group. In this study, the patients were assigned clinic visits every two weeks rather than every three to four months, thus providing positive reinforcement of their insulin and dietary regimes.[5]

Hemoglobin A1c is thus the current gold standard by which glucose control is measured with a target value of <7.0% by the American Diabetes Association (ADA) and <6.5 by the American College of Clinical Endocrinology (ACCE). However, hemoglobin A1c is merely an average of blood glucose over a period of time and does not address variability. Essentially, the A1c is the average of a summation of the area under and above the peaks and troughs of glycemic variability. For example, a person with type 1 diabetes may spike a postprandial glucose of 250 mg/dL, then fall in the interprandial period to 50 mg/dL before rising again. This would give an average value of 150 mg/dL that roughly equates to an A1c of 6.5% to 7.0%, implying good control. Figure 1 is a composite tracing of a person with diabetes whose A1c was measured at 6.7%. Moreover, the A1c is adversely affected by red cell survival with falsely high values occurring in cases of increased survival and certain hemoglobinopathies and falsely low values occurring with increased red cell turnover and certain anemic states.[6-8] The A1c value, in addition, is difficult for the patient to comprehend.[9] This has led the ADA to propose the use of a calculated value, the estimated average glucose, which is reportedly easier to understand and more meaningful for the patient.

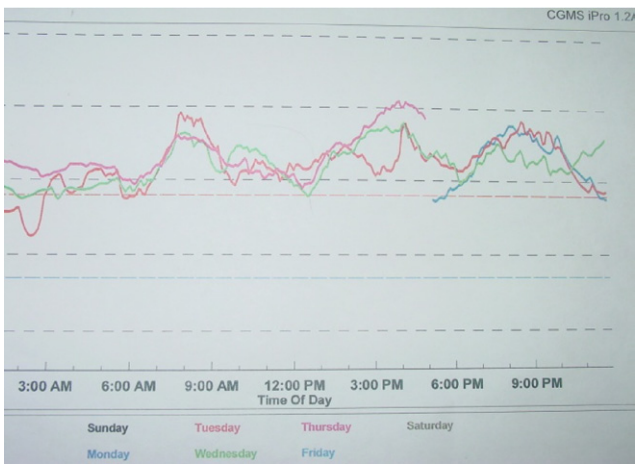


**Figure 1** Composite tracing of glycemic excursions.

Recent attention has focused on postprandial glucose spikes as a possible cause of the vascular changes in people with diabetes who are in seemingly good control. In vitro experiments have shown that short-term repeated exposure to high glucose levels causes adverse cellular responses when compared with cells exposed to a consistent glucose load or constantly high levels of glucose.[10] These short but significant glucose elevations trigger the release of free radicals such as superoxide, hydroxyl, peroxyl, alkoxyl, and hydroperoxyl, to name a few, which act on the endothelium. This postulate has been further evaluated by numerous epidemiological studies, which suggest that postprandial hyperglycemia may be a unique risk factor for the development of diabetic cardiovascular disease.[11-14] The Diabetes Intervention Study in 1996 concluded that postprandial hyperglycemia was a better predictor of subsequent myocardial infarction and mortality than fasting hyperglycemia. They also surmised that A1c is "not the most complete expression of the degree of glycemia."[14] Other researchers have concluded that acute glucose variations including upward (postprandial) and downward (interprandial) deviations can be considered as risk factors for cardiovascular events.[15] It is therefore more important to pay attention to the postprandial glucose than the fasting glucose or the A1c not only early on in the course of the disease but also throughout the life of the patient.

Several researchers have confirmed more conclusive evidence of postprandial oxidative stress. Measuring oxidative byproducts in the urine, numerous studies have confirmed increased free radical production in both poorly and seemingly well-controlled diabetics when compared with nondiabetics.[16]

Oxidative stress has also been implicated in the development of diabetic neuropathy. During periods of short-term glucose elevation, mitochondrial oxidative stress has been shown to cause neuronal death in vitro by way of superoxide formation and inhibition of aconitase and lipid peroxidation within one hour of its occurrence. Through an intrinsic feedback mechanism, antioxidant production occurs and serves to prevent excessive destruction during periods of sustained hyperglycemia. This period of antioxidant production, however, requires three to six hours. Once the blood glucose level declines to normal, short-term antioxidant production stops, thus leaving the neurons unprotected and subjecting them to further injury during the next brief period of hyperglycemia. In addition to direct nerve damage from oxidative stress, microvascular damage decreases oxygen and nutrient supply, causing further damage and impairing regeneration.[17]

There is also evidence linking small nerve fiber dysfunction with hyperglycemia and the development of skin and

foot ulcerations, as well as impaired wound healing secondary to microvascular damage, which decreases available oxygen, impairing nerve fiber regeneration. Small-cell fiber involvement has been reported to precede the development of large fiber damage in the development of diabetic polyneuropathy. Although all of the peripheral nervous system is involved in diabetic polyneuropathy, there is "an association between small cell nociceptor nerve fiber dysfunction and microvascular blood flow abnormalities."[18–21]

It therefore becomes imperative to look further than A1c when counseling and treating patients with diabetes. Combining A1c with the GlycoMark, a US Food and Drug Administration (FDA)-approved test that targets postprandial hyperglycemia, is an option but, once again, patient comprehension of the values and their significance remains a stumbling block.

Three-day continuous glucose monitoring systems offer a decided advantage in the treatment of diabetes mellitus, uncovering unrecognized hypoglycemia, a major patient safety concern, and in secondary disease prevention.[22] There are several different types of monitors available, all of which have been approved by the FDA for adjunctive use in the treatment of diabetes mellitus. All of the available monitors work by way of a small subcuticular electrode and use glucose oxidase to measure interstitial glucose levels. The monitors were initially used for the treatment of type 1 diabetes, particularly those difficult to control and prone to hypoglycemia and ketoacidosis. Given the knowledge that oxidative stress accounts for complications in both type 1 and type 2 diabetics, however, more frequent measurement of glucose values and in particular postprandial excursions would be beneficial in the management of this disease.

In the steady state, there is a small difference in measured blood and interstitial glucose values. At times of rapidly rising or falling glucose levels, interstitial values may lag behind by as much as 10 minutes because of physiologic delay. This is a major limitation for the real time monitors, generally used in conjunction with an insulin pump, because calibration cannot be done during periods of extreme glycemic excursions. This also is a limitation for the blinded monitor, although it is not as critical.

Minor limitations to interstitial monitoring include pain at the insertion site, skin reactions, bleeding, failure to record, dislodging, and patient over-compliance during the monitoring period with a blinded monitor.

Two types of subcutaneous continuous glucose monitors are currently available. Real-time monitors communicate with the patient's home glucose monitor or a built-in monitor, with readily accessible data. Blinded monitors store all data in a recorder over the period the sensor is worn and require a computer for downloading the data. Table 1 illustrates the features of the five available types.

Seven-point self-glucose monitoring has been proposed in type 1 diabetics as a method of improving control. In this manner, the patient would record three preprandial, three 2-hours postprandial, and one bedtime blood sugar value. In clinical practice, this is impractical and, for all intents and

**Table 1** Current available subcutaneous monitors

| Sensor | Type | Interstitial glucose range | Sensor saturation time | Interstitial glucose recordings | Calibration | Alarms | System requirements | Maximum sensor duration | FDA age approval | Notes |
|---|---|---|---|---|---|---|---|---|---|---|
| Dexcom Plus Seven | Real time | 40-400 mg/dL | 2 hours | Every 5 minutes | Every 12 hours | High/Low | Sensor, receivers, transmitter, home glucose monitor | 7 days | 18 | Acetaminophen may falsely elevate readings |
| Guardian | Real time | 40-400 mg/dL | 2 hours | Every 5 minutes | Every 12 hours | High/Low | Sensor, receivers, transmitter, home glucose monitor | 3 days | 7 | |
| I-Pro | Blinded | 40-400 mg/dL | 2 hours | Every 5 minutes | N/A | N/A | Sensor and recorder | 3 days | N/A | Computer and software needed |
| Free Style Navigator | Real time | 20-500 mg/dL | 10 hours | Every minute | 10, 12, 24, and 72 hours | High/Low | Sensor, receiver and transmitter | 5 days | 18 | Glucose monitor built in |
| Paradigm | Real time | 40-400 mg/dL | 2 hours | Every 5 minutes | Every 12 hours | High/Low | Sensor, receivers, transmitter, home glucose monitor | 3 days | 7 | |

purposes, impossible. "Increased frequency of finger sticks (over 8 per day) could lead to similar diagnostic results and therapeutic decisions as continuous (glucose) data, but are difficult to implement in clinical practice."[9]

Through a small puncture in the skin overlying the abdomen, a capillary sensor is placed in the patient's interstitial fluid. Attached to the sensor is an external semipermeable membrane and attached to that is a recorder. Figure 2 shows the sensor and recorder placed on a patient's abdomen. The enzyme glucose oxidase in the semipermeable membrane reacts with glucose and oxygen in the interstitial fluid to produce gluconic acid and hydrogen peroxide. Hydrogen peroxide degrades and yields two electrons that are captured by the recorder. This reaction occurs every five minutes or 288 times for each 24-hour period. After a three-day interval, the sensor and recorder are removed, the sensor discarded, and the stored information downloaded onto a computer. Using specialized software, the information is printed as a sensor summary including total number of glucose values recorded; percentage of time above, at, or below normal; pie charts; a daily detail summary; and a modal day summary, the latter two being line graphs.

During the period the monitor is worn, patients are asked to maintain their usual diet, activities, and medications and to truthfully record the time, type, and quantity of each meal and of each snack. In addition, they are required to record at least four self-glucose values to be compared with the values obtained by the continuous glucose monitor. Although these values differ slightly, this allows an evaluation of their monitor and techniques.

Once downloaded and printed, the continuous tracing are reviewed by the physician and compared with previous glucose and A1c values, with comments recorded in the patient's chart. It is most important to first search for episodes of hypoglycemia that can be unrecognized by the patient because of autonomic dysfunction. Figure 3 is a tracing of an insulin-dependent diabetic with early morning hypoglycemia and Figure 4 is a person with diabetes who took a short-acting secretogogue without eating. After this,

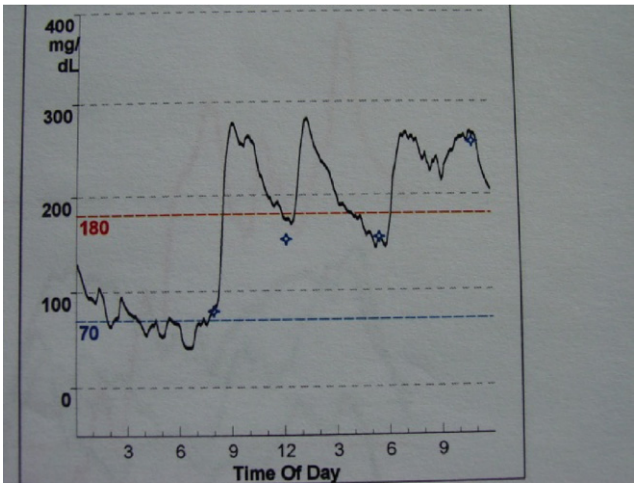


**Figure 3** Early morning hypoglycemia.

the tracings are reviewed for glycemic spikes and the patient's general baseline glucose level. The effects of meals, medications, and activity on the patient's diabetic control can easily be evaluated and noted in the chart.

After the review, the patients, their spouses, and/or children, if possible, are brought back to the office for a discussion and explanation of the tracings. It is frequently helpful to have other family members in attendance to aid in understanding the data and to encourage compliance. At this time, the attendees are able to directly see the effect that diet, medications, and activity have upon glucose excursions. A brief explanation of glycemic spikes and oxidative stress and their relationship to secondary disease complications is also done. Adherence to diet, medication compliance, and exercise is stressed. Should there be a problem identified that can be corrected by dietary adjustment, an appointment can be scheduled with a clinical dietician. If necessary, recommendations for medication adjustment or changes can be made, this time with a much better degree of certainty, and explained to the patients in "layman's" terms.

At the end of the consultation, the patients are asked to record at least one 2-hour post-prandial glucose value daily

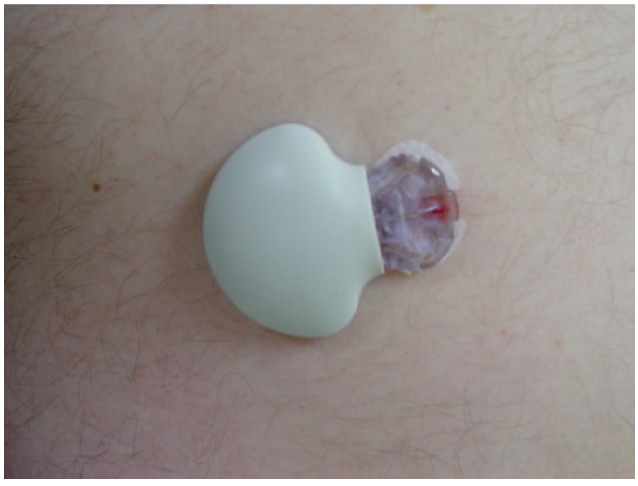

**Figure 2** Sensor and recorder in place.

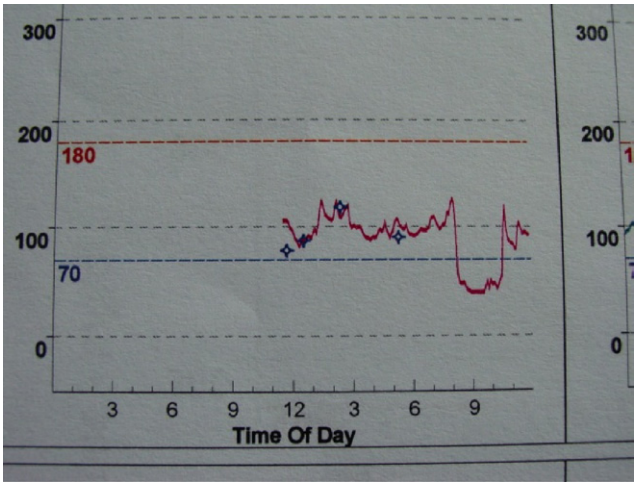


**Figure 4** Late evening hypoglycemia.

for a month, as well as keep a food diary, and to bring these to their next office visit. This serves to involve them and their family in the treatment of their disease, fosters self-control, and encourages compliance.

In conclusion, although A1c remains the current benchmark or gold standard of diabetic control, there is increasing evidence that short-term glucose excursions play a major role in the development and progression of secondary diabetic complications. Use of continuous glucose monitoring offers the physician and patient valuable information in the treatment and control of diabetes and in the prevention of its complications.

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