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EDITORIAL

The Benefits of Implanted Glucose Sensors

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The most information about the constantly changing glucose levels in diabetes can be obtained though continuous glucose monitoring. Based on currently available glucose sensing technology, implanted glucose sensors offer the best combination of features of all types of continuous glucose monitors. Continuous glucose monitoring can be applied to a variety of situations, including management of diabetes, as well as treatment of trauma patients and other people with temporarily elevated glucose levels. Implanted glucose sensors have limitations and require engineering advances to match the accuracy of many established physiological monitors. Many of these advances will likely utilize nanotechnology.

The best way to monitor a situation when the outcome is very important is with a continuously running security camera rather than with an intermittently functioning high-quality reflex camera. Likewise, the best way to monitor changes in glycemia is with a continuous glucose monitor rather than with an intermittent blood glucose (BG) monitor. A standard blood glucose monitor for self-monitoring blood glucose provides discrete highly accurate BG levels; however, these readings do not predict future BG levels and effort is needed to make each measurement. Such a monitor generates a sufficiently small number of readings per day that most patients and physicians can appreciate patterns for many weeks and months of data. A continuous glucose monitor, however, provides multiple moderately accurate glucose levels, as well as trend information, and multiple measurements are made automatically without any incremental effort for the multiple assays that are made each hour. When the direction and magnitude of change for glucose levels are known, then a continuous monitor can be programmed to predict whether excessively high or low glucose levels are likely to occur over the next 15–30 minutes.[1] These monitors generate so many hundreds of data points per day that it is almost impossible to study every data point to analyze glycemic trends without computerized software.

Five main types of enabling technologies are being utilized to develop continuous glucose monitors. These approaches to continuous monitoring involve (1) implantable subcutaneous sensors, (2) microdialysis of skin, (3) noninvasive glucose monitors of skin, (4) noninvasive ocular glucose monitors, and (5) intravenous sensors for hospital use. The last four of these methods have thus far been plagued to various extents by problems of prolonged lag between blood and interstitial fluid glucose levels during dynamic glucose fluctuations, inadequate accuracy, safety concerns, and/or poor portability. Only implantable subcutaneous sensors have reached a sufficient level of performance for several products of this category to be approved by the U.S. Food and Drug Administration (FDA) and to become available to consumers.

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The list of currently approved and readily available continuous glucose monitors includes the CGMS Gold (Medtronic Diabetes, Northridge, CA); the Guardian Real Time and Paradigm Link, which share the same sensor component (Medtronic Diabetes); and the Seven (Dexcom, San Diego, CA). The Navigator (Abbott Diabetes Care, Alameda, CA) is currently being reviewed by the FDA.

Continuous glucose monitors serve four main purposes in the management of diabetes. These monitors are useful in (1) detecting and predicting hyperglycemia in real time, (2) detecting and predicting hypoglycemia in real time, (3) assessing mean glycemia, and (4) determining the amount of glycemic variability.

An episode of hyperglycemia in a patient with diabetes can require hours or days of intensive therapy to return the blood glucose value to normal. The number and severity of hyperglycemic episodes cumulatively contribute to an increase in the mean blood glucose level and to the magnitude of glycemic variability. Both of these measures of glycemia are risk factors for microvascular complications. An automatic real-time monitor can detect frankly elevated glucose levels and predict impending elevated glucose levels based on the absolute glucose level and the magnitude of a rise in the glucose level. This information can allow the patient to take action to bring down the glucose level. All of the FDA-approved continuous glucose monitors lack a primary indication. This means that if a patient is considering a response to a reading from a continuous glucose, it is then necessary to measure a self-monitored blood glucose level and take action based on this blood glucose level, not on the continuous glucose level.

An episode of hypoglycemia in a patient with diabetes puts the patient in acute danger of brain or heart damage. Hypoglycemia can be a medical emergency and is a common cause of visits to emergency departments by insulin-requiring patients with diabetes. Hypoglycemic episodes contribute to glycemic variability, but their effect on depressing the hemoglobin A1C level may go unnoticed unless such patient's hemoglobin A1C falls so much that it is low enough to be in the normal range and below the range generally seen in even mild diabetes. A real-time glucose monitor with an alarm can alert a patient to impending hypoglycemia and trigger a behavioral response to avert the problem. Several studies have demonstrated a trend of fewer hyperglycemic and hypoglycemic glucose readings and a greater number of midrange glucose levels in patients with diabetes who had access to real-time continuous glucose monitoring data, even without specific instructions in some cases.

Any tool for managing diabetes is intended to decrease the incidence of complications. To the extent mean glycemia is a risk factor for these complications, then a goal of any diabetes tool should be to lower the mean glycemic level toward the normal range. Continuous glucose monitors have been shown in many uncontrolled and nonrandomized trials, as well as in a few randomized controlled trials, to lower the hemoglobin A1C level over a period of use of 3–6 months in most cases. Whereas continuous glucose monitoring is by definition a tool for monitoring a patient, the information that this technology provides could potentially not only decrease the number of hyperglycemic and hypoglycemic episodes, but also decrease the mean glucose levels as well.

Many insurance payers are calling for evidence that this new technology lowers mean glycemia in order to provide coverage. Multiple trials of continuous glucose monitoring have demonstrated improvement in mean glycemia. However, almost all of these trials have been dismissed by many health insurance payers for one of several deficiencies, including being uncontrolled, unblinded, inadequately powered, too short in duration, not statistically significant, not clinically significant, or not consistent with benefit.[2] The perfect trial that will convince payers has not been conducted. A rigorous attempt to demonstrate the benefits of continuous glucose monitoring is currently being undertaken by a team of expert diabetes clinicians with funding from the Juvenile Diabetes Research Foundation. The Randomized Study of Real-Time Continuous Glucose Monitors in the Management of Type 1 Diabetes is a randomized controlled two-phase study of the use of continuous glucose monitors in the management of type 1 diabetes mellitus. This 11-site study began recruiting in December 2006 and intends to enroll 450 adults and children as subjects. The first part of the study will compare the effects of real-time continuous glucose monitoring and close contact with the health care providers with self-monitoring of blood glucose and close contact with the health care providers as well. The second part of this study will follow both of the groups of subjects on the same regimen, which will be real-time continuous glucose monitoring and limited contact with health care providers. The primary outcome measures at both 6 and 12 months will be (1) hemoglobin A1C level, (2) episodes of severe hypoglycemia, (3) percentage of sensor values in the range of 60–180 mg/dl, (4) number of sensor values below 70 mg/dl, (5) quality of life indices, and (6) magnitude of glycemic variability as expressed by such statistics as mean amplitude of glycemic excursions, standard deviation, and mean rate of change (http://clinicaltrials.gov/ct/show/NCT00406133).

Subcutaneous continuous glucose monitoring provides accurate readings in intensive care patients. The automatic nature of these measurements can save valuable time for hospital nurses and ensure that measurements are made on time. Several systems are currently under development for the hospital market for automatic continuous glucose monitoring of venous blood. These devices will be inserted in line with an intravenous catheter and will (1) withdraw blood, (2) measure the blood glucose concentration using a traditional monitor, and (3) dispose of the blood through a side port off of a t-tube connector. Three hurdles will need to be overcome for continuous glucose monitoring to become viable. It will be necessary to demonstrate that (1) subcutaneous glucose values are representative of blood glucose values in hospitalized patients, given that shifts in blood pressure and skin perfusion and development of peripheral edema might alter the relationships between subcutaneous glucose and glucose levels[3]; (2) clinical benefits of these systems accrue, given that the use of continuous intravenous sampling necessitates precluding access to one dedicated large-bore vein for other purposes; and (3) time savings accrue, given that current FDA-approved continuous glucose monitors all lack a primary indication and a nurse would still have to check a finger stick blood glucose value if therapy was required.

Subcutaneous glucose sensors are the ideal tool for measuring glycemic variability, which is a recently recognized risk factor for diabetic microvascular disease. Glycemic variability has been linked to oxidative stress, which is linked to vasculopathy. The deleterious effect of rapid and large fluctuations in glycemia is independent of the harmful effect of elevated mean glycemic levels, as reflected by elevated hemoglobin A1C and mean blood glucose concentrations. Glycemic variability has been linked to oxidative stress, which is linked to vasculopathy.[4] The link between glycemic variability and oxidative stress has been reported from only a single laboratory to date, and no randomized controlled outcome studies have been conducted to assess the impact on oxidative stress markers (let alone on frank vascular events) from decreasing glycemic variability in patients with diabetes. Continuous glucose monitoring is the best tool for assessing glycemic variability. Several statistical measures have been developed to express this concept. These measures include mean amplitude of glycemic excursions, blood glucose risk index, and glucose rate of change.

Although continuous glucose monitoring is already being utilized in many clinical states, the currently available implantable glucose sensors could benefit from improved engineering in at least four areas that would lead to improved performance. First, greater accuracy is needed. The point accuracy of currently approved products has a mean average relative difference in the range of 16%.[2] This suboptimal degree of point accuracy may lead to suboptimal readings in trend direction and magnitude, as evidenced by discordance in comparisons of simultaneously measured glucose readings on the same subject. When tested under optimal conditions, consumer blood glucose monitors will generally have a median relative absolute difference around 5%.[5] Second, faster tissue equilibration is needed. Currently available and likely-soon-to-be-available implanted glucose oxidase sensors require a run-in period of 2–10 hours, during which time measurements cannot be made. The exact mechanism for this period of sensor instability has been postulated to be a local reaction related to tissue injury at the site of implantation.[6] Third, a longer period of implantation is needed. Current continuous glucose monitoring devices are approved for between 3 and 7 days. The inconvenience of using these devices would decrease if they did not require such frequent replacement. Fourth, better transmission of data is needed. Currently available and likely-soon-to-be-available implanted glucose sensors can project readings wirelessly to their dedicated monitor if it is 5–10 feet away. For military and some civilian indications, a much greater range for data transmission would be useful. The safety of implanted radio frequency identification transmitters has been recently questioned in the press. Research is now needed to address these concerns.

Nanotechnology may provide solutions to sensor performance problems. Nanotechnology can lead to the development of new materials that can be used in sensors, including (1) sensor materials such as carbon nanotubules, which could lead to better sensor performance; (2) better tolerated biomaterials that could mitigate the local immunogenic and fibrotic response to implanted hardware such as implanted sensors; and (3) better sensor coatings to stimulate local blood flow and decrease the lag time between blood glucose and interstitial fluid glucose levels.

Accurate implanted continuous glucose monitors are needed. These devices will provide around-the-clock information on absolute glucose values and trends. These devices will be useful for monitoring the metabolism of people with diabetes, as well as the metabolism of soldiers. Better sensors are needed. I expect that advances in nanotechnology will provide solutions and improve sensor performance.

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