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SYMPOSIUM

The Current Environment of CGM Technologies

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Introduction

This presentation discusses the technology involved in continuous blood glucose monitoring, focusing on the various classes of sensors. It also includes some potential uses for continuous glucose data now and in the future.

Overview of CGM Technology

Direct versus Indirect Measurement

Direct glucose measurements measure a specific property of glucose, which must be distinguished from any similar properties in other molecules. Measurable properties of glucose include measures of its spectral, chemical, and competitive binding profiles.

Indirect measurements of glucose measure its effect on other properties. For example, glucose seems to change the resistance of the skin to a radio frequency signal so the Pendra device measures glucose via radio frequency impedance. The Orsense device measures Rouleax formation, a "stacking" of red blood cells in small blood vessels, in response to glucose. The Glucon device indirectly measures glucose by looking at the sound created by tissue expansion when heated rapidly by light.

Direct measurements tend to be more predictable than indirect ones because the signal being measured is usually unique and interferences more predictable. With indirect measurements, the signal is often not unique; there are many chemicals and other substances within the body that may produce the same signal. For example, glucose affects the refractive index of the eye and this effect can be measured indirectly. However, every optically active chemical in the body that goes through a blood vessel also has the potential to change the refractive index of the eye.

Implantable Sensors

Implantable sensors are still years away because of issues relating to biocompatibility and the risks inherent to surgical placement of these devices in blood vessels. Most of these sensors are glucose oxidase based; however, others are based on competitive binding or spectral properties.

Glucose Oxidase

Glucose oxidase-based sensor technology depends on the reaction of glucose with oxygen in the presence of glucose oxidase to create gluconic acid. The glucose oxidase enzyme is regenerated after it reduces oxygen to hydrogen peroxide. In most sensor systems, the hydrogen peroxide is then oxidized specifically by a hydrogen peroxide electrode causing the movement of electrons which can be measured. Measurement of glucose through glucose oxidation is highly specific in that virtually nothing cross-reacts with glucose oxidase. However, there are potential interferences with the electrode.

The limitation of using this method in an implantable sensor is that the reaction requires one oxygen molecule for each glucose molecule. Glucose is present in the body at vast molar excess over oxygen so oxygen is the limiting reagent, not glucose, and a simple glucose oxidase sensor implanted in the body would measure oxygen levels not glucose levels. To prevent this, implantable sensors must somehow give oxygen an advantage over glucose. The DexCom implantable device does this by using a GORE membrane; blood vessels grow right into the membrane, providing the necessary oxygen supply. The device transmits its glucose measurements to an external radio frequency receiver. Tests show that 96% and 97% of its readings fall within the

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Abbreviations: (AGP) ambulatory glucose profile, (CGM) continuous glucose monitoring, (S4MS) Sensors for Medicine and Science, (FDA) Food and Drug Administration, (ROC) receiver operating characteristic, (SMBG) self-monitoring of blood glucose

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Clarke Error Grid A & B Zones, respectively, after it has been calibrated and compared to self-monitoring of blood glucose (SMBG) and YSI analysis.

A brief note on measuring accuracy: Traditionally, having 95% of readings in the A & B Zones of an Error Grid was considered an acceptable level of accuracy for a continuous blood glucose monitoring device. As devices have become more accurate this may need to be reconsidered. Measurements in the extremes of the B Zone readings are often very inaccurate (i.e. a reading of 170 with a reference value of 71 is a B on the Clarke Error Grid). My personal belief is that while having 95% of readings within the A & B Zones is an acceptable level of accuracy, 85-90% of those readings should be in the A Zone.

Competitive Binding

There is a clever technology from Sensors for Medicine and Science (S4MS) which uses glucose binding to "quench" fluorescence from a reporter molecule. The sensor capsule shines a light against the fluorescent binding molecule, which sends a signal back to a detector. When glucose is bound to the molecule the fluorescent signal is decreased, so as glucose levels increase the measured fluorescence decreases. The resulting glucose calculations are transmitted to a radio frequency receiver.

Spectral

The Animas implantable device uses spectroscopy to measure glucose. A miniaturized sensor is implanted in a blood vessel where it detects small changes in glucose levels. A larger device, which houses a laser generator and performs signal analysis, is located within a closed compartment under the skin. Its infrared laser signal is transmitted to and then returned from the miniaturized sensor in the blood vessel for data processing.

Needle Sensors

The needle sensor from Medtronic was the first needle sensor available on market. Based on glucose oxidase, it is currently in its second generation with the CGMS Gold system, which utilizes a three-day sensor. The sensor reads interstitial glucose every five minutes, maintains up to 10 days worth of data, and can be downloaded by the healthcare professional. The overall error is approximately 15% when evaluated by independent investigators. Currently, the system is indicated for adjunctive use, which means it cannot be used to make clinical decisions about insulin dose. The patient or healthcare provider must perform a test with a blood glucose meter to evaluate the glucose value used when taking a mealtime insulin dose.

The Medtronic Guardian RT device is a wireless system that uses a three-day sensor and displays glucose values every five minutes. It also features high and low threshold alarms. Medtronics recently introduced a version of this system that combines the Guardian RT glucose sensor with an insulin pump.

The FreeStyle Navigator from Abbott Diabetes Care uses glucose oxidase but not oxygen to detect interstitial glucose levels. The electrode has a long carbon chain that holds both glucose oxidase and an osmium mediator, called a wired enzyme. After glucose has reduced the glucose oxidase the enzyme passes its electrons to the osmium mediator rather than oxygen. The mediator then passes the electrons to the electrode for measurement. This is very interesting because it avoids using oxygen and thus the requirement for a limiting membrane on the sensor. This could ultimately lead to a much more accurate system.

The FreeStyle Navigator device is wireless and utilizes a 5-day sensor. The initial calibration period is 10 hours. Early data show inaccuracies to be in the 11-13% range when the system is used in a clinical setting and 14-17% when used by patients. The FreeStyle Navigator system has not received Food and Drug Administration (FDA) approval.

The Isense system uses a 7-day glucose oxidase electrode. The device has a reported inaccuracy rate of approximately 17%.

The GlucoDay S device from A.Menarini Diagnostics uses microdialysis to measure glucose. A microdialysis tube is inserted into the abdominal wall and connects a micropump to a biosensor. The micropump pumps a perfusion solution through the tube; as the fluid flows through the tube under the patient's skin it picks up glucose through the dialysis membrane and is transported to the biosensor and is there measured for glucose content. Glucose levels are measured every three minutes for 48 hours, the duration of the sensor's intended use in-clinic. Real-time blood glucose readings are shown on the monitor and can be downloaded to a computer for analysis. The device also features a programmable alarm. An independent measurement of accuracy showed that the device had an inaccuracy of approximately 13%.

Noninvasive Transcutaneous Sensors

There are a number of transcutaneous methods to measure glucose: reverse iontophoresis; intercellular fluid sampling; and measurement of dermal characteristics such as photoacoustics, radio frequency impedance, and refractive index.

Iontophoresis

The first continuous glucose monitoring (CGM) device to receive FDA approval was the GlucoWatch. Although its process is often described as reverse iontophoresis, it actually measures bulk flow of glucose across a membrane. The device utilizes an electrical charge to pull sodium and chloride out of the patient's skin; glucose is passively pulled along with the water of hydration of the salts. The extracted solution is then oxidized and measured for glucose content. Overall the device has an error rate of approximately 17-20%. The sensor measures glucose levels every ten minutes but only has a 12-hour half-life so it must be changed twice per day. Also, it causes significant skin irritation. It is approved for sale in the US.

There are other devices in development that use transcutaneous methodology, such as the SpectRx system. This device creates a small hole in the skin, places a cap on the puncture, and then draws up small amounts of fluid over the next three days, measuring the amount of glucose in the fluid. In a similar fashion, Bayer Diagnostics is working on a device that uses sonic force to disrupt the skin. Intercellular fluid from the wound would then be collected and measured for glucose.

Photoacoustics

The Glucon device uses an interesting methodology called photoacoustics. This involves applying laser light to the skin above a blood vessel, causing a small but rapid increase in temperature in the blood vessel and making a soft popping sound. The device "listens" to the pop and determines glucose levels from the acoustic characteristics of the sound. Unlike the other systems, which measure interstitial glucose, the Glucon actually measures blood glucose. The device is not yet approved by the FDA and is not for sale in the US.

Light Scattering

The GlucoLight device is a non-invasive sensor that uses µScatter (microscatter) to measure the scatter of light from cells to determine glucose levels in interstitial fluid. Like the Glucon device, the GlucoLight system is not yet approved by the FDA.

Summary

There are a wide variety of continuous devices available now and in the near future. These systems have limited static accuracy (approximately 15-20%) compared with traditional blood glucose meters; however, they offer much more information about the patient's glucose trends. The key is to learn how to use these systems properly.

Using Continuous Data Today and Tomorrow

Understanding the Past

Reviewing glucose trend data from continuous glucose monitoring provides patients with an opportunity to identify patterns of poor control and then determine ways to improve their control. Unfortunately, patterns are not always easily identified and often there are no apparent patterns.

Several years ago, Drs. Roger Mazze and David Rodbard developed a method of glucose data analysis called the ambulatory glucose profile. The method was never widely adopted because most patients were not testing at the necessary high frequency. Now, with continuous monitoring, patients can gather enough data points to utilize the method.

Essentially, the ambulatory glucose profile (AGP) provides a mean value across the day. All of the values from multiple days are shown on a single time scale from midnight to midnight. The average for each period is shown along with a standard deviation. As shown in **Figure 1**, the mean value is represented by the orange line and the standard deviation around it is shaded in blue. The profile in this example shows relatively small standard deviation variability from midnight to noon. "Fine-tuning" control during times of lower variability (green area) can be achieved through pharmacologic therapy adjustment. However, periods of extreme variability (red area) may also require lifestyle interventions. With the availability of CGM data, the AGP can be a valuable tool for evaluating glycemic control.

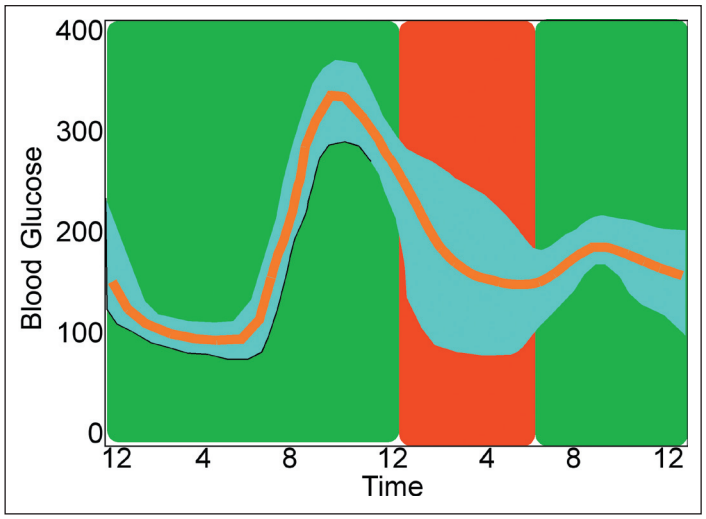

Figure 1. Analysis of Ambulatory Glucose Profile

The Present

The availability of CGM data not only allows for more effective pattern recognition and therapeutic intervention, it also provides information for planning daily insulin dosages. Patients who take insulin calculate their dosage using a general formula based on their food intake and current blood glucose level.

Can patients use CGM devices to make this calculation? First, it is important to note that none of the CGM devices currently available have FDA approval for replacement of SMBG; they cannot be used to calculate a dose without SMGM confirmation. However, for the sake of discussion, we will look at the differences between SMBG and CGM data in terms of calculating a bolus insulin dose.

We know that the accuracy of most CGM devices is in the 14-20% error range whereas the error range for SMBG meters is 5-7%. This means that if a patient had a blood glucose level of 50 mg/dL, a typical SMBG device would have a 95% confidence range of 43-57 mg/dL but a CGM device would have a larger range of 29-71 mg/dL. Assuming the patient has an insulin sensitivity factor of 30, calculating the bolus dose using the SMBG device could result in a dosage that is off by up to one quarter of a unit. Using the CGM data would result in a dosage that is off by up to three quarters of a unit.

In the lower glucose ranges, these differences are not particularly significant; however when glucose is extremely elevated the error rates become quite significant. For example, if the true glucose is 400 mg/dL, the SMBG device could read 340-460 mg/dL while the CGM device could show 232-586 mg/dL. The error in dosage using SMBG would be approximately 2 units off compared to an error of approximately 5 units using CGM.

However, it is important to remember that the other component of monitoring is the trend in glucose level. Knowing glucose trends is so important that it compensates for any differences in accuracy. Glucose values change rapidly over time. Data from the GlucoWatch shows that glucose changes at a rate of approximately +1 mg/dL/min to -1 mg/dL/min in 50% of the readings. Glucose may change as much as +2 mg/dL/ min to -2 mg/dL/min in 90% of the readings. In some instances, the maximum rate of change can be as high as 5 mg/dL per minute. With such variability, it is much more valuable for a patient to know the trend in their glucose level than to know their current level. With the trend, they can predict what their blood sugar will be after the 60-90 minutes it takes for injected insulin to have an effect. This is one primary advantage of CGM technology over traditional SMBG.

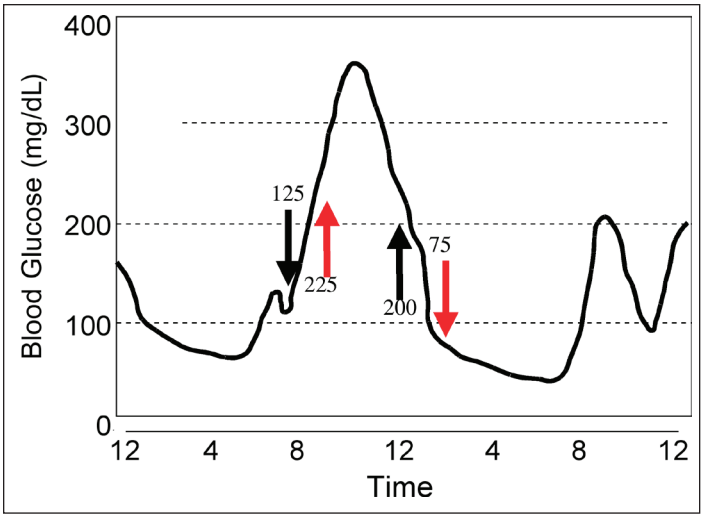

Figure 2. Profile of patient glucose variability.

Figure 2 shows data from a patient whose pre-breakfast glucose was 125 mg/dL. However, his glucose was approximately 225 mg/dL by the time his insulin started working. Had the patient known where his glucose would eventually be, he would have increased his dosage accordingly. Because his pre-lunch glucose was now 200 mg/dL, he added a correctional dose to his usual bolus. However, by the time the insulin started working, his glucose had already dropped to 75 mg/dL. In short, the ability to calculate insulin dosages based on future glucose levels provides a much safer and more effective way of achieving glycemic control.

The Future

Some key issues to consider when looking to the future of continuous glucose monitoring relate to how we can better predict hypoglycemia or adjust basal insulin rates. There is also the question of when a closed-loop system will finally be available.

Trade-Off Between Sensitivity and Specificity

There are a lot of predictive algorithms currently available; some are much more complicated than others. However, in every algorithm, the focus is on sensitivity and specificity. Sensitivity refers to how well the device predicts hypoglycemia while specificity refers to its ability to detect hypoglycemia. Sensitivity and specificity are measured using Receiver Operating Characteristic (ROC) curves. This method was developed in the 1950's as a by-product of research on interpreting radio signals contaminated by noise.

Within the context of hypoglycemia predictions, ROC curves allow us to look at the trade-off between sensitivity and specificity. Are patients willing to be bothered with false alarms (sensitivity) if the device detects 100% of actual hypoglycemic events (specificity)? If a patient is hypoglycemic every third night, is he willing to be woken up three or four times per night in order to pick up that one event? This is a question that each individual must decide.

Adjusting Basal Insulin Rates

A key concern with CGM is that patients will begin micro-adjusting their basal rates. With continuous sensors, patients will see their glucose every few minutes and may chose to take small bursts of insulin to lower elevated blood glucose between meals. Although they will be instructed to confirm glucose levels with SMBG before making any adjustments, they will need better algorithms and training about how to make insulin adjustments without overcorrecting.

Conclusion

Currently available continuous glucose monitoring systems lack the accuracy of blood glucose monitoring. However, the benefit of having glucose trend data makes them more useful than blood glucose monitoring for making decisions about insulin therapy. They also can be used for preventing hypoglycemia; however, sensitivity and specificity must be considered.