FEATURE

Emerging Technology for the Improved Management of Diabetes

Written by Emma Hitt, PhD

Many patients with diabetes are faced with the challenge that their disease requires constant awareness and monitoring of blood glucose levels, with the fear of entering hypoglycemia. W. Kenneth Ward, MD, Oregon Health and Science University, Portland, Oregon, USA, presented the concepts of artificial pancreas therapy and some basic science behind glucagon in the artificial pancreas system.

The basic structure of the artificial pancreas system is that sensed data from a continuous glucose monitor is transmitted to a controller that delivers commands to insulin and glucagon pumps. Currently, the system is not truly closed loop; as in many cases, better control is achieved by announcing the meal and administering a priming insulin dose.

There are several types of controllers for artificial pancreas systems. The proportional integral derivative (PID) and PID-like algorithm systems use an algorithm to calculate the required insulin dose, while a model-based system can take into account emotional stress, medical stress, and medications. Other systems include the fuzzy logic approach and hybrid approaches.

A recent crossover study evaluated the response of a PID-like control system that had a model-based adaptive component, to determine if the addition of the model-based characteristic could improve hyperglycemia [Youssef JE et al. *J Diabetes Sci Technol* 2011]. Patients with the adaptive PID-like system demonstrated lower blood glucose levels than patients with the PID-like system without an adaptive component over a 13-hour period.

The concept underlying a bihormonal artificial pancreas system is prevention of hypoglycemia. Although patients with type 1 diabetes have intact α cells in the pancreas, the regulation of glucagon secretion is abnormal, resulting in insufficient glucagon secretion during hypoglycemia [Lorenzi M et al. *West J Med* 1984]. Suddenly decreasing insulin is not effective because the effect of insulin is slow. In contrast, the effect of glucagon is very fast. In a single-blinded, study of type 1 diabetics, patients received insulin plus placebo or insulin plus glucagon [Castle JR et al. *Diabetes Care* 2010]. The proportional derivative algorithm used for administering glucagon was either low-gain or front-loaded higher gain. Patients who received glucagon experienced fewer hypoglycemic events (mean 15 minutes/day) compared with patients who received placebo (mean 40 minutes/day). Front-loaded glucagon delivery resulted in fewer threats of hypoglycemia, which is defined as the trigger of glucagon, and actual hypoglycemic events compared with low-gain delivery. However, in some cases, glucagon does not work and other measures, such as a meal, are required to stabilize glucose levels [Castle J et al. *J Diabetes Sci Technol* 2010]. Dr. Ward suggested that, in some cases, perhaps the problem is not the glucagon, but that the sensor is not providing accurate information to the controller.

Ronald Tamler, MD, PhD, MBA, Mount Sinai Diabetes Center, New York, New York, USA, discussed the use of mobile phones to support the practice of medicine. A meta-analysis of 22 studies that evaluated the use of mobile phones to aid in the management of diabetes demonstrated an overall HbA1C reduction of 0.5% [Liang X et al. *Diabetic Med* 2011]. In a subanalysis, patients with type 2 diabetes experienced a greater HbA1C response than patients with type 1 diabetes, who showed no effect. However, these studies were performed prior to the market release of smart phones.

Of all the new phones released into the market, 75% are smart phones and over 125 million people in the United States currently use a smart phone [comScore 2013]. Dr. Tamler suggested that a smart phone app can help patients follow the 5 "Ms" of Adherence: 1) messaging to improve health literacy, 2) motivation to empower patients, 3) monitoring to track results, 4) money to track and optimize the affordability of a treatment regimen, and 5) mobility to streamline patient care [Bloomgarden Z, Dagogo-Jack S. *J Diab* 2011].

An app search for "diabetes" yields in 600 results for an iPhone and 480 results for an Android phone [Eng DS, Lee JM. *Ped Diab* 2013]. Dr. Tamler stated that the best apps for diabetes management that are currently available include Diabetes Buddy, Track 3 Diabetes, and Glucose Buddy for the iPhone, and OnTrack Diabetes, Glucool, Track3, and Glucose Buddy for Android phones. In addition, there is a United States Food and Drug Administration (FDA)-approved app for the medical management of type 2 diabetes, called Welldoc [Quinn CC et al. *Diabetes Care* 2011]. To use Welldoc, patients must have an invitation, so that an employer or health insurance pays a monthly premium for the patient. Dr. Tamler pointed out that the role of the FDA should be to draft guidelines regarding the design of apps that will be used as an accessory to a medical device or sensor, that also allows patient input.

David C. Klonoff, MD, Diabetes Research Institute, Mills-Peninsula Health Services, San Mateo, California, USA, discussed several emerging types of sensors for glucose monitoring, including electrochemical sensors for subcutaneous use, fluorescence sensors for subcutaneous use, and spectroscopy.

Dr. Klonoff highlighted several barriers of electrochemical subcutaneous glucose sensors: interfering substances, oxygen dependence, and biofouling and encapsulation. The body may reject the implanted sensor and will respond through the process of biofouling—coating the sensor with proteins, cells, etc—and/or encapsulation with a "wall." Several advancing developments have worked to reduce these barriers. For example, coating the sensor with a hydrogel, surface patterning with nano technology, or anti-inflammatory coatings can prevent biofouling. Developers must keep these barriers in mind when designing an effective sensor. A recently developed glucose sensor contains 5 layers: 1) an outer hydrogel membrane to prevent biofouling; 2) catalase to break down hydrogen peroxide (a by-product of breaking down glucose at electrode); 3) a polyurethane coating to limit glucose influx; 4) glucose oxidase, the enzyme that breaks down glucose; and 5) hatched surface to prevent analytes from reaching electrode [Vaddiraju S et al. *J Diab Sci Technol* 2011].

Dr. Klonoff highlighted that nano technology is now being employed in emerging sensors. With a high surface area-to-volume ratio, it allows more signals and more rapid analyte movement to occur. The types of nano materials used in sensors include nano particles, carbon-nano tubes, nano rods, nano wires, and nano composites.

Fluorescence for glucose sensing is an emerging technology that measure fluorescence decay lifetime (FDL), which is a measure of the amount of time it takes for the emission of fluorescence. FDL is not affected by tissue scattering, fluctuating signal strength, or interfering substances because analyte concentration is not important for FDL measurements, time is. Glucose attaches to a dye or a carrier molecule that holds the dye, which either results in fluorescence or quenches fluorescence. Disadvantages of the fluorescence technology are that the dyes are potentially toxic to humans, implants are subject to a foreign-body response, and the fluorescent dyes are sensitive to pH.

Spectroscopic, noninvasive monitors have been approved for use in Europe. The challenge for spectroscopic sensors is that they sense a small signal that is easily disrupted by interference of other biological surfaces or molecules.

Recent advances in diabetes research have resulted in multiple new technologies that hold promise in helping patients to manage diabetes. Improved management may help improve glucose control, reduce hypoglycemic events, and improve convenience and quality of life for patients living with the disease.

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