Key Artificial Pancreas Advances Are in the Works

BY MIRIAM E. TUCKER
Senior Writer

BETHESDA, MD. — A fully "closed-loop" insulin pump delivery system is still several steps away, but steady progress is being made toward the creation of a functional artificial pancreas that provides far better glucose control for type 1 diabetic patients than is currently available.

That was the consensus from a meeting sponsored by the National Institutes of Health and the Juvenile Diabetes Research Foundation in which scientists, clinicians, and industry representatives came together to address the current state of the art and to discuss ways of overcoming technical obstacles.

Over the last 2 decades, external insulin pump therapy has become a standard treatment option for patients with type 1 diabetes. Current pumps are "open loop," meaning that they require input from the user, both in setting the background (basal) infusion rate and for delivering premeal boluses based on the blood glucose level and anticipated carbohydrate consumption. Recent advances have incorporated a continuous glucose monitor into the system along with algorithms that estimate the bolus dose, but the technology still requires user input—and therefore is subject to some degree of error.

'The development of a closed-loop artificial pancreas is the most likely candidate to revolutionize the treatment of childhood type 1 diabetes.'

The main problem isn't in delivering the insulin. Rather, it's overcoming the numerous technical barriers to developing a real-time sensor that can respond to the current glucose level, as well as its rate and direction of change. Moreover, algorithms linking the sensor with the delivery system must also account for all the other physiologic factors that contribute to glucose homeostasis, such as incretins, free fatty acids, and counterregulatory hormones.

"There are three elements to a closed-loop system: the delivery device, the sensing device, and linking algorithms. Each element is very complex, and difficult to develop. Each must really be developed independently before you can put together a complete closed-loop system," explained Dr. Christopher D. Saudek, professor of medicine at the Johns Hopkins University and director of the Johns Hopkins Diabetes Center, Baltimore.

But Dr. Saudek, who has been researching open-loop implantable pumps for the last 25 years, still sees mechanical insulin delivery as more immediately promising than a biological approach such as islet or stem cell transplantation. "Either would be a cure if it worked reliably and well. But the biological approach still requires enormous basic science breakthroughs before it will help people. The mechanical approach is applied research. It's a matter of refining techniques we have that work."

The preference for mechanical "cure" certainly applies to children and adolescents, for whom the need for lifelong immune suppression following transplantation is undesirable, said Dr. William V. Tamborlane, professor of pediatrics and chief of pediatric endocrinology at Yale University, New Haven, Conn.

Maintaining good diabetes control is particularly difficult in adolescents, and not just because they tend to be rebellious and noncompliant. Teenagers experience wide swings in glucose because their unique physiology makes them more insulin resistant while paradoxically more vulnerable to hypoglycemia, especially at night. "The development of a closed-loop artificial pancreas is the most likely candidate to revolutionize the treatment of childhood type 1 diabetes in the foreseeable future," Dr. Tamborlane said.

He reviewed preliminary results of short-term (30-35 hours), closed-loop control in seven adolescents with type 1 diabetes, using Medtronic Minimed's external glucose sensor and infusion pump (information about both available at www.minimed.com). With a slight upward adjustment ofthe overnight algorithm—from a glucose target of 90-120 mg/dL—it was relatively easy to maintain steady glucose levels and avoid hypoglycemia during sleep.

However, despite multiple premeal infusion adjustments, peak postmeal blood glucose levels often exceeded 200 mg/dL, particularly after breakfast.

Currently under investigation is "semi-automatic" or "hybrid" strategy, where the patient manually administers a partial, priming dose of insulin prior to eating, with the remaining insulin regulated by the system. Although not closed loop, this would be a great improvement over currently available technology, Dr. Tamborlane noted.

The same would be true of an imperfect completely closed loop: "Now, when my patients forget to bolus, their blood glucose goes up to 400 [mg/dL]. At least with a closed loop, it would only go to 250. … Maybe we don't need to aim for perfect," he said.

Similar postmeal problems were seen among 22 young adults with type 1 diabetes in whom a system developed by Roche Diagnostics (www.roche-diagnostics.com) was tested in Germany, said Dr. Guido Freckmann, of the Institute for Diabetes Technology at the University of Ulm.

This system utilized an empirical glucose-control algorithm based on a calculation of the current glucose concentration and its gradient, the remaining effect of already-infused insulin, the amount of carbohydrate intake, and patient-specific factors such as basal insulin requirement and insulin-to-carbohydrate ratio. As with the adolescents, overnight values approached the target of 120 mg/dL, with only half the variability that occurred among the patients without the controller. But blood glucose values remained highly variable throughout meal times, again particularly after breakfast.

"Our data suggest that a semi-closed loop system using the subcutaneous route for glucose measurement and insulin application is possible. Although the time delay of insulin action means that a 'feed-forward' insulin dose is necessary, during nighttime the feedback part of the algorithm is able to achieve good control," Dr. Freckmann said.

Indeed, such time delays will always occur with sensors that monitor glucose in the interstitial fluid, according to Dr. Jeffrey I. Joseph, director of the Artificial Pancreas Center at Thomas Jefferson University, Philadelphia.

Minimed Medtronic has been developing a glucose sensor that measures changes in the oxygen concentration within the superior vena cava, where it is implanted for the long term. Using the vascular sensor and a peritoneal implantable insulin delivery device, French researchers have demonstrated the feasibility of a closed-loop system.

Although the physiological delay with this system is tiny, here the problem is longevity. From a practical standpoint, any implantable device would need to work for at least 7 years to be viable. Currently the Minimed system must be replaced every 12-16 months, Dr. Joseph noted.

Since 1996, he has been working with another major insulin pump manufacturer, Animas (www.animascorp.com), to develop a long-term implantable optical glucose sensor based on near-infrared absorption spectroscopy at multiple wavelengths. Optical monitoring has the potential to overcome the biocompatibility limitations of all other electrochemical sensors, and both animal and human studies have demonstrated rapid response time and sufficient accuracy. However, miniaturization has thus far proved to be "a technical challenge," Dr. Joseph said.

At least two other companies are forging ahead with continuous glucose sensors. Abbott's Navigator, currently under review by the Food and Drug Administration, would be used to make therapeutic decisions, although calibration by the user would still be required (www.abbottdiabetescare.com). Dexcom Corp. (www.dexcom.com) is developing a sensor for long-term implantation in the subcutaneous tissue, with the ultimate aim of coupling it with an insulin delivery system. ■

Small Thyroid Nodules May Pose Greater Risks Than Large Ones

CHICAGO — Solid thyroid nodules smaller than 1 cm in diameter tend to carry a greater risk of papillary carcinoma than do larger nodules, Dr. Nagesh Ragavendra reported at the annual meeting of the Radiological Society of North America.

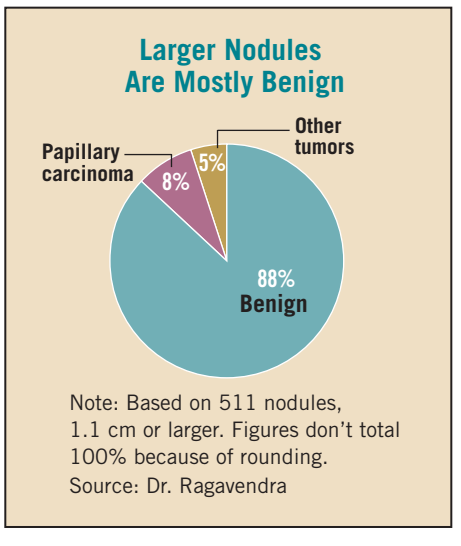
The results of this study using fine-needle nonaspiration need to be confirmed in larger investigations as the study was too small to prove statistical significance. But the trend was marked, Dr. Ragavendra said.

The risk was 16% for thyroid nodules 1 cm or less in diameter compared with 8% for nodules 1.1 cm or more.

Surprisingly, the study also found that capsular invasion is relatively common in solid thyroid nodules, said Dr. Ragavendra, professor of radiology and chief of the ultrasound section at the University of California at Los Angeles. Five of the larger-sized nodules had capsular invasion; two had nodal metastases.

Biopsies were performed under ultrasound guidance on 598 focal thyroid nodules in 466 consecutive patients using the fine-needle nonaspiration technique with on-site cytologic examination.

With this technique, cells are extracted with a 25-gauge needle that is repeatedly and rapidly advanced into and withdrawn from the nodule. The needle is not connected to external suction, as is the case with traditional fine-needle aspiration.



Note: Based on 511 nodules, 1.1 cm or larger. Figures don't total 100% because of rounding.
Source: Dr. Ragavendra

Neither technique has proved superior in the cytopathologic studies of thyroid nodules. But it is suggested that fine-needle nonaspiration provides specimens with larger numbers of cells and better preserved cytomorphology, Dr. Ragavendra said.

The sample tends to be less blood tinged with nonaspiration than with aspiration fine-needle biopsy, Dr. Ragavendra added. Further, nonaspiration allows continuous monitoring of the position of the needle tip, thus ensuring proper sampling of the area of interest.

Of the 511 nodules that were 1.1 cm in diameter or larger, histology revealed that 448 (88%) were benign, 39 (8%) were papillary carcinoma, and 24 (5%) were other tumors.

Of the 87 nodules 1 cm or less, 67 (77%) were benign, 14 (16%) were papillary carcinoma, and 6 (7%) were other tumors.

The findings of the investigation do not settle the long-standing debate as to which thyroid nodules should be biopsied. But those with some cystic components tend to be benign, Dr. Ragavendra said. At UCLA, all solid nodules, whether hypoechoic or isoechoic, are candidates for fine-needle biopsy.

—Patrice Wendling