Novel artificial pancreas successfully controls blood sugar more than 24 hours

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An artificial pancreas system that closely mimics the body's blood sugar control mechanism was able to maintain near-normal glucose levels without causing hypoglycemia in a small group of patients. The system, combining a blood glucose monitor and insulin pump technology with software that directs administration of insulin and the blood-sugar-raising hormone glucagon, was developed at Boston University (BU). The first clinical trial of the system was conducted at Massachusetts General Hospital (MGH) and confirmed the feasibility of an approach utilizing doses of both hormones. In their report, appearing in *Science Translational Medicine*, the researchers also found unexpectedly large differences in insulin absorption rates between study participants, differences they were able to account for by adjustments to the system.

"This is the first study to test an artificial pancreas using both insulin and glucagon in people with type 1 diabetes. It showed that, by delivering both hormones in response to frequent blood sugar tests, it is possible to control blood sugar levels without hypoglycemia, even after high-carbohydrate meals," says Steven Russell, MD, PhD, of the MGH Diabetes Unit, who co-led the research team with Edward Damiano, PhD, of the BU Department of Biomedical Engineering.

In type 1 diabetes, the insulin-producing beta cells of the pancreas are destroyed by the immune system, requiring insulin treatment to regulate blood sugar levels. Intensive glucose control involving frequent blood sugar testing and insulin administration can delay or prevent long-term complications - such as retinal damage, kidney failure, or cardiovascular disease - but is extremely demanding and difficult to maintain. Continuous glucose monitors and insulin pumps can help, but patients remain at risk for hypoglycemia, a potentially life-threatening drop in blood sugar caused by too much insulin.

Because any administration of insulin, even by an artificial pancreas system, has been associated with the risk of hypoglycemia, BU investigators Damiano and lead author Firas El-Khatib, PhD, developed a system that both accounts for the rate of insulin absorption and also incorporates glucagon, a hormone naturally released by the pancreas to raise blood sugar levels. While the alpha cells of the pancreas that produce glucagon are not destroyed in people with type 1 diabetes, the cells no longer release glucagon in response to low blood sugar.

"Large doses of glucagon are used as a rescue drug for people with severely low blood sugar," explains Damiano. "Our system is designed to counteract moderate drops in blood sugar with minute doses of glucagon spread out throughout the day, just as the body does in people without diabetes." In 2007 Damiano's team tested the system in diabetic pigs, which led to FDA approval of the human trial.

The current study enrolled 11 adults with type 1 diabetes and was primarily designed to test the software that controls the system. To get the most accurate glucose levels, the system used a monitor that directly reads blood sugar through a sensor placed into a vein instead of a continuous glucose monitor that takes readings under the skin. Participants' blood sugar was controlled by the system for 27 hours, during which time they ate three standardized, high-carbohydrate meals and slept through the night at the hospital. While the system kept glucose levels close to the target range for six participants, five others experienced hypoglycemia significant enough that they needed a dose of orange juice to raise their blood sugar.

Close analysis of participants' blood-insulin levels revealed a nearly fourfold difference in the rate at which individuals absorbed and cleared the fast-acting insulin used in the study, with some rates of absorption being much slower than anticipated. Since the controlling software determined dosage

based on the expected rate of insulin absorption, participants who absorbed at a slower rate received excessive doses, leading to hypoglycemia. A test of participants' response to a single insulin injection verified that some had consistently slow and some consistently fast rates of insulin absorption. Rates of absorption also varied too much from experiment to experiment, even on an individual basis, to allow participant-specific dosage calculations.

After globally adjusting the software parameters to a slower insulin absorption rate, the researchers conducted repeat experiments in the same participants. This time none of the slow-absorption participants experienced hypoglycemia significant enough to require intervention. Blood-sugar levels were only slightly higher in repeat experiments involving participants with fast insulin absorption, showing that the adjusted software parameters were effective for all study participants and may be adequate for everyone with type 1 diabetes. The elimination of episodes of hypoglycemia in repeat experiments involving the same participants affirmed that the initial mismatch between parameter settings and insulin absorption rate had been the cause of the hypoglycemia. All previous reported studies of artificial pancreas systems have included episodes of hypoglycemia, but this is the first study to confirm and address the cause of that hypoglycemia.

Later this spring the researchers will begin a follow-up study with a system using the revised settings and driven by an FDA-approved continuous glucose monitor. Those experiments will last more than 48 hours and include children as well as adults. The investigators also plan to compare the insulin/glucagon system with a version that uses only insulin. "The device we ultimately envision will be wearable and incorporate a glucose sensor inserted under the skin that communicates wirelessly with a pump about the size of a cell phone," says Russell, who is an instructor in Medicine at Harvard Medical School. "The pump would administer insulin and probably glucagon, and would contain a microchip that runs the control software."

Damiano, whose 11-year-old son was diagnosed with type 1 diabetes at the age of 1, adds, "A system like this would replace the need for people to constantly check their blood sugar and to make treatment decisions every few hours. It would need to be maintained but could take over the decision-making process, closely emulating a functioning pancreas. It wouldn't be a cure, but it has the potential to be the ultimate evolution of insulin therapy for type 1 diabetes." Damiano is an associate professor of Biomedical Engineering at Boston University.

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