New islet transplant method leads to insulin independence

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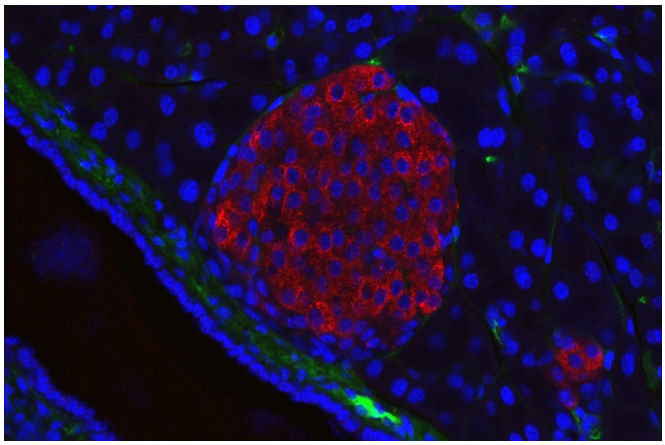

A pancreatic islet from a mouse in a typical position, close to a blood vessel; insulin in red, nuclei in blue. Credit: Generated in the Solimena lab, Paul Langerhans Institute Dresden

More than half of the most seriously affected type 1 diabetes patients achieved years of insulin independence after they received a new method of islet cell transplantation, according to a paper published in *Diabetes Care* on the long-term outcomes of two Phase 3 clinical trials.

In addition to finding that many patients didn't need insulin to maintain their blood sugar for up to eight years, the authors, co-led by Michael Rickels, MD, the Willard and Rhoda Ware Professor in Diabetes and Metabolic Diseases in the Perelman School of Medicine at the University of Pennsylvania, also reported that the new approach necessitated fewer transplants than typical and was exceedingly safe.

"These data are important in showing that in the long run, islet transplantation has efficacy, including among those who have had kidney transplants," said Rickels. "Yes, most type 1 diabetes patients are improved tremendously with current insulin delivery systems. But for those having the most difficulty controlling their blood sugar, and those whose diabetes has already been complicated by needing a kidney transplant, the outcomes we saw in this study are what we've been hoping to achieve for more than 20 years."

Two cohorts of patients were analyzed: Those who received just islet transplantation (48) and those who received islets after kidney transplantation (24). Of those observed all the way through to what was defined as the "long-term" endpoint (up to eight years for islet-only, and seven for those who also had kidney transplants), more than half had surviving islet grafts. Additionally, of the 75 percent who initially were able to come off insulin therapy, more than half maintained total insulin independence, meaning they needed no additional insulin injections throughout the years of follow-up.

Islet cells are located in the pancreas and are critical to keeping blood sugar in check by producing the hormone insulin. But the islets of those with type 1 diabetes are destroyed by the immune system and don't make insulin. A form of cell replacement therapy—which exists elsewhere in the world (such as in Australia, Canada, the United Kingdom, and many parts of Europe) but is still considered experimental in the United States—is islet cell transplantation, which takes normal-functioning cells from the pancreases of deceased donors and introduces them via a small catheter to patients whose own islets no longer work.

Rickels; Ali Naji, MD, Ph.D., the J. William White Professor of Surgical Research; and the multi-institution Clinical Islet Transplantation Consortium have been working since 2004 to establish optimized and standardized methods for islet isolation and transplantation, and to demonstrate its safety and efficacy as a novel cell therapy for the treatment of type I diabetes.

Their approach has included T-cell depletion to

induce immunosuppression combined with anti-inflammatory, anti-coagulation, and early intensive insulin therapies to prevent the transplanted islets from being damaged or stressed before a new blood supply from the liver is established, making the process of islet engraftment and survival more efficient.

This new approach was performed with 72 patients who volunteered, all of whom had type I diabetes and "impaired awareness hypoglycemia," which meant that they had incidents of severely low blood sugar that occurred when they weren't aware of it, which can result in a seizure or loss of consciousness. A group had also had previously undergone kidney transplantation as a result of their diabetes. Essentially, these patients were among the most critically affected by the disease.

When it came to measuring the safety of the process, important because of the severity of disease in the patient population, the researchers found that there were 104 "serious adverse events"—which effectively meant hospitalization for anything that could range from dehydration to an infection—for the total patient population in the study after receiving islets. While their study didn't allow for a control group who didn't receive islet transplantation to compare directly, Rickels said the number of adverse events was much lower than could be expected for a similar patient population.

"These are the most seriously affected patients, and you'd be expecting to see some hospitalizations in a population managed on immunosuppression therapy," Rickels said. "It's important to note that none of the adverse events were related to the actual islet product. Also, kidney function remained stable during long-term follow-up in both cohorts, in fact improving in those who had kidney transplants. Overall, this is a much less invasive procedure that opens itself up to significantly fewer complications than what many of these patients would otherwise require, a pancreas transplant, which involves major abdominal surgery."

A particularly impactful finding, Rickels said, was that this study showed their method was achieving success while using fewer donor pancreases.

"Currently, around the world, there's an expectation of two-to-three donor pancreases being needed," Rickels said. "Here, it's one, maybe two. It's a much more efficient protocol, and opens up access for more islet transplantation as a hoped-for alternative to pancreas transplants."

Rickels and colleagues plan to submit their data as part of a biologic license application to the Food and Drug Administration (FDA) to make their islet transplantation technique an approved treatment for patients like those in the trials.

More information: Michael R. Rickels et al, Long-term Outcomes With Islet-Alone and Islet-After-Kidney Transplantation for Type 1 Diabetes in the Clinical Islet Transplantation Consortium: The CIT-08 Study, *Diabetes Care* (2022). DOI: 10.2337/dc21-2688

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