Pancreatic Islet Transplantation

National Diabetes Information Clearinghouse

National Institute of Diabetes and Digestive and Kidney Diseases

NATIONAL INSTITUTES OF HEALTH

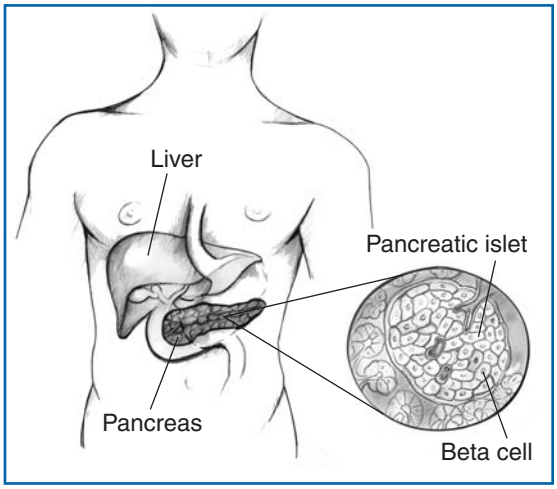
What are pancreatic islets?

The pancreas, an organ about the size of a hand, is located behind the lower part of the stomach. It makes insulin and enzymes that help the body digest and use food. Throughout the pancreas are clusters of cells called the islets of Langerhans. Islets are made up of several types of cells, including beta cells that make insulin.

Insulin is a hormone that helps the body use glucose for energy. Diabetes develops when the body doesn't make enough insulin, cannot use insulin properly, or both, causing glucose to build up in the blood. In type 1 diabetes—an autoimmune disease—the beta cells of the pancreas no longer make insulin because the body's immune system has attacked and destroyed them. A person who has type 1 diabetes must take insulin daily to live. Type 2 diabetes usually begins with a condition called insulin resistance, in which the body has difficulty using insulin effectively. Over time, insulin production declines as well, so many people with type 2 diabetes eventually need to take insulin.

What is pancreatic islet transplantation?

In an experimental procedure called islet transplantation, islets are taken from the pancreas of a deceased organ donor. The islets are purified, processed, and transferred into another person. Once implanted, the beta cells in these islets begin to make and release insulin. Researchers hope that islet transplantation will help people with type 1 diabetes live without daily injections of insulin.



The pancreas is located in the abdomen behind the stomach. Islets within the pancreas contain beta cells, which produce insulin.

Research Developments

Scientists have made many advances in islet transplantation in recent years. Since reporting their findings in the June 2000 issue of the *New England Journal of Medicine,* researchers at the University of Alberta in Edmonton, Canada, have continued to use and refine a procedure called the Edmonton protocol to transplant pancreatic islets into selected patients with type 1 diabetes that is difficult to control. In 2005, the researchers published 5-year follow-up results for 65 patients who received transplants at their center and

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reported that about 10 percent of the patients remained free of the need for insulin injections at 5-year follow-up. Most recipients returned to using insulin because the transplanted islets lost their ability to function over time. The researchers noted, however, that many transplant recipients were able to reduce their need for insulin, achieve better glucose stability, and reduce problems with hypoglycemia, also called low blood sugar.

In its 2006 annual report, the Collaborative Islet Transplant Registry, which is funded by the National Institute of Diabetes and Digestive and Kidney Diseases, presented data from 23 islet transplant programs on 225 patients who received islet transplants between 1999 and 2005. According to the report, nearly two-thirds of recipients achieved "insulin independence"—defined as being able to stop insulin injections for at least 14 days—during the year following transplantation. However, other data from the report showed that insulin independence is difficult to maintain over time. Six months after their last infusion of islets, more than half of recipients were free of the need for insulin injections, but at 2-year follow-up, the proportion dropped to about one-third of recipients. The report described other benefits of islet transplantation, including reduced need for insulin among recipients who still needed insulin, improved blood glucose control, and greatly reduced risk of episodes of severe hypoglycemia.

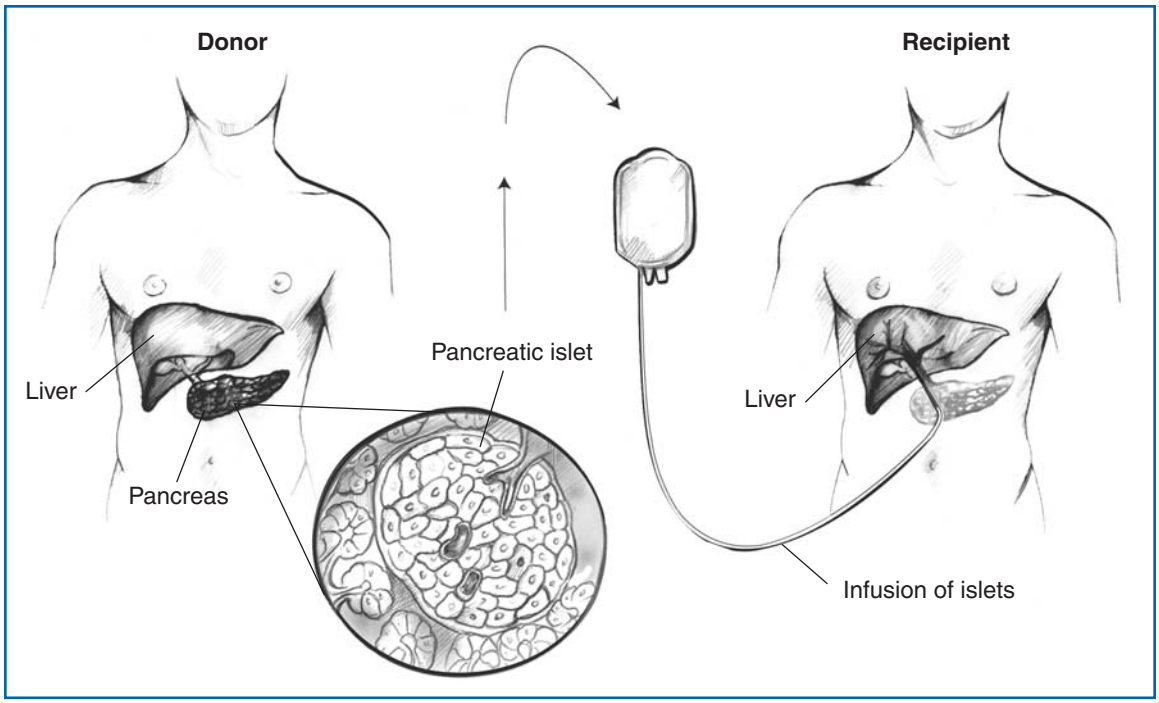
In a 2006 report of the Immune Tolerance Network's international islet transplantation study, researchers emphasized the value of transplantation in reversing a condition known as hypoglycemia unawareness. People with hypoglycemia unawareness are vulnerable to dangerous episodes of severe hypoglycemia because they are not able to recognize that their blood glucose levels are too low. The study showed that even partial islet function after transplant can eliminate hypoglycemia unawareness.

Transplant Procedure

Researchers use specialized enzymes to remove islets from the pancreas of a deceased donor. Because the islets are fragile, transplantation occurs soon after they are removed. Typically a patient receives at least 10,000 islet "equivalents" per kilogram of body weight, extracted from two donor pancreases. Patients often require two transplants to achieve insulin independence. Some transplants have used fewer islet equivalents taken from a single donated pancreas.

Transplants are often performed by a radiologist, who uses x rays and ultrasound to guide placement of a catheter—a small plastic tube—through the upper abdomen and into the portal vein of the liver. The islets are then infused slowly through the catheter into the liver. The patient receives a local anesthetic and a sedative. In some cases, a surgeon may perform the transplant through a small incision, using general anesthesia.

Islets begin to release insulin soon after transplantation. However, full islet function and new blood vessel growth associated with the islets take time. The doctor will order many tests to check blood glucose levels after the transplant, and insulin is usually given until the islets are fully functional.



Islets extracted from a donor pancreas are infused into the liver. Once implanted, the beta cells in the islets begin to make and release insulin.

What are the benefits and risks of islet transplantation?

The goal of islet transplantation is to infuse enough islets to control the blood glucose level without insulin injections. Other benefits may include improved glucose control and prevention of potentially dangerous episodes of hypoglycemia. Because good control of blood glucose can slow or prevent the progression of complications associated with diabetes, such as heart disease, kidney disease, and nerve or eye damage, a successful transplant may reduce the risk of these complications.

Risks of islet transplantation include the risks associated with the transplant procedure—particularly bleeding and blood clots—and side effects from the immunosuppressive drugs that transplant recipients must take to stop the immune system from rejecting the transplanted islets.

Immunosuppressive Drugs

Rejection is the biggest problem with any transplant. The immune system is programmed to destroy bacteria, viruses, and tissue it recognizes as "foreign," including transplanted islets. In addition, the autoimmune response that destroyed transplant recipients' own islets in the first place can recur and attack the transplanted islets. Immunosuppressive drugs are needed to keep the transplanted islets functioning.

The Edmonton protocol introduced the use of a new combination of immunosuppressive drugs, also called anti-rejection drugs, including daclizumab (Zenapax), sirolimus (Rapamune), and tacrolimus (Prograf). Daclizumab is given intravenously right after the transplant and then discontinued. Sirolimus and tacrolimus, the two main drugs that keep the immune system from destroying the transplanted islets, must be taken for life or for as long as the islets continue to function. These drugs have significant side effects and their long-term effects are still not fully known. Immediate side effects of immunosuppressive drugs may include mouth sores and gastrointestinal problems, such as stomach upset and diarrhea. Patients may also have increased blood cholesterol levels, hypertension, anemia, fatigue, decreased white blood cell counts, decreased kidney function, and increased susceptibility to bacterial and viral infections. Taking immunosuppressive drugs also increases the risk of tumors and cancer.

Researchers continue to develop and study modifications to the Edmonton protocol drug regimen, including the use of new drugs and new combinations of drugs designed to help reduce destruction of transplanted islets and promote their successful implantation. These therapies may help transplant recipients achieve better function and durability of transplanted islets with fewer side effects. The ultimate goal is to achieve immune tolerance of the transplanted islets, where the patient's immune system no longer recognizes the islets as foreign. If achieved, immune tolerance would allow patients to maintain transplanted islets without long-term immunosuppression.

Researchers are also trying to find new approaches that will allow successful transplantation without the use of immunosuppressive drugs. For example, one study is testing the transplantation of islets that are encapsulated with a special coating designed to prevent rejection.

Shortage of Islets

A major obstacle to widespread use of islet transplantation is the shortage of islets. Although organs from about 7,000 deceased donors become available each year in the United States, fewer than half of the donated pancreases are suitable for whole organ pancreas transplantation or for harvesting of islets—enough for only a small percentage of those with type 1 diabetes. However, researchers are pursuing various approaches to solve this problem, such as transplanting islets from a single donated pancreas, from a portion of the pancreas of a living donor, or from pigs. Researchers have transplanted pig islets into other animals, including monkeys, by encapsulating the islets or by using drugs to prevent rejection. Another approach is creating islets from other types of cells, such as stem cells. New technologies could then be employed to grow islets in the laboratory.

For More Information

For information about clinical trials in islet transplantation, see *www.ClinicalTrials.gov* or *www.citregistry.org*.

You may also find additional information on this topic using the following databases:

The NIDDK Reference Collection is a collection of thousands of materials produced for patients and health care professionals, including fact sheets, brochures, and audiovisual materials. Visit *www.catalog.niddk.nih.gov/resources*.

MedlinePlus brings together a wealth of information from the National Library of Medicine, the National Institutes of Health, and other government agencies and health-related organizations. MedlinePlus offers easy access to medical journal articles, a medical dictionary and medical encyclopedia, health information in Spanish, hospital and physician directories, drug and supplement lists, interactive patient tutorials, links to hundreds of clinical trials, and the latest health news. Visit *www.medlineplus.gov*.

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