Islet Cell Transplantation and Alternative Therapies

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KEYWORDS

• Pancreas transplantation • Islet transplantation • Type 1 diabetes • Beta cells

KEY POINTS

- Pancreas and islet cell transplantation are therapeutic options for patients with type 1 diabetes suffering severe hypoglycemia or worsening complications despite advanced medical therapy.
- Some countries like Canada have both therapies available as accepted medical treatment, whereas in the United States, islet transplantation remains experimental for type 1 diabetes.
- The advances and improvements achieved, especially since 2000, brought this therapy much closer to the clinical use.

In recent years, as the obesity epidemic plateaued, the new cases of type 2 diabetes also slowed down in United States.[1] Unfortunately, in contrast, a nearly 30% increase in the rates of type 1 diabetes in children aged 14 and younger has been reported.[2] According to the US Centers for Disease Control and Prevention, if current trends continue, we will see 23% of type 1 diabetes by 2050. The United States is not alone in this; studies from Europe, Canada and Australia have reported the same trends, largest increases being observed in children under 5 years old.[3] Even though clinical management of type 1 diabetes has improved beyond imagination with the advances in technology, improvements of insulins, and insulin delivery devices, as well as glucose monitoring systems, prevention and cure are the 2 major challenges for future generations of scientists facing this increase in the numbers. This article reviews the advances we achieved on the way to cure type 1 diabetes.

Currently, pancreas transplant is an option for patients with type 1 diabetes who need more help than medical therapy can offer. This is a common practice for patients undergoing kidney transplantation or less commonly as a therapy alone. Performed first in 1966 by Kelly and colleagues,[4] this replacement therapy has now much improved outcomes; for example, the expected 1-year pancreas graft survivals are

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90% with simultaneous pancreas and kidney (SPK) transplantation, 83% in pancreas after kidney transplantation, and 80% with pancreas transplantation alone, according to the latest accumulated data from scientific registry of transplant recipient. However, it remains a late therapeutic option in advanced disease because it is a major surgery with complications[5] and patients become lifetime dependent on immunosuppression to prevent rejection.

The need for improvement inspired the clinical and scientific community to find a method to separate endocrine tissue, which is only 1% of the pancreas from the rest of bulky exocrine tissue, to develop islet transplantation therapy.

Islet replacement therapy has 2 arms, allogeneic islet transplantation involving harvested islets from deceased organ donors, used in type 1 diabetes patients, and autotransplantation, which is performed after total pancreatectomy using extracted islets from the individual's own pancreas to prevent or reduce the severity of diabetes after removal of the gland.

Improvement of the isolation techniques have taken decades, and advances observed today are the result of the collaborative effort of many who spent their career in this field. The earliest recorded attempt is transplantation of sheep pancreas injected under skin in 1893.[6] Around 1965, isolation of islets mainly used for research purpose was reported by Moskalewski.[7] Few years later, in 1972, Ballinger and Lacy[8] isolated normal islets and performed successful transplant to restore euglycemia in diabetic rat models. Almost a decade later, the first results from a series of type 1 diabetes patients receiving islet transplantation, by Sutherland and colleagues,[9] was published from the University of Minnesota. Unfortunately, none became insulin independent at the time. But around 1989, clinically successful islet transplantation was achieved, although lasting only 1 month.[10] The following decade until 2000 witnessed attempts of islet transplantation therapy with less than 10% success of insulin independence.[11]

The Edmonton protocol published around 2000 by Shapiro and colleagues[12] was a landmark study that advanced this field once more. The researchers reported that all 7 patients in this study achieved insulin independence at 1 year. The Edmonton protocol separated itself from its predecessors by 4 main variations. The protocol included a steroid-free immunosuppressive regimen, using combinations of sirolimus, low-dose tacrolimus, and an anti-CD25 antibody daclizumab, which enabled them to eliminate the glucocorticoids that was heavily relied on previously. The second variation included the use of a sufficient number of viable islets from multiple donors, as many as 4 to provide enough islets, 10,000 islet equivalents per kilogram, infused usually several weeks apart, instead of the previously used number of 6000 islet equivalents per kilogram. A third point of difference was seen in their isolation and purification method modified by removing nonhuman medium to minimize exposure to xenoproteins. Last, to optimize islet function, they limited the cold storage time to less than 13 hours, by eliminating previous method of culturing the cells several days before the infusions. In 2001, the group published their observation for a median follow-up of 10 months: 11 of 12 patients were reported to be insulin independent (4 with normal glucose tolerance, 5 with impaired glucose tolerance, and 3 with levels in the diabetic range).[13]

A collaboration was born after this new development, bringing multiple international centers together in a multicenter trial supported by the National Institutes of Health and the immune tolerance network. This consortium initiated series of pilot studies around 2004, the Clinical Islet Transplantation Consortium (CIT) currently has 2 phase III studies, CIT-07 for type 1 diabetes with severe hypoglycemia and glycemic lability and CIT-06, which includes type 1 diabetics with kidney transplantation.[14]