Review

HUMAN PANCREATIC ISLET TRANSPLANTATION

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ABSTRACT

Various studies have concluded that the prevention and progression of chronic microvascular complications associated with type 1 diabetes can be accomplished by daily multiple insulin injections, to maintain near normal normoglycemia to physiological limits. This regime is unable to mimic the normal pulsatile secretion of insulin. Pancreatic islet transplantation, which involves the transplantation of specific isolated islets holds promise in this endeavor. The isolation and purification of islet cells before transplantation is major hurdle in this process. To minimize the immunogenicity of the transplanted islets, highly purified islet preparations of proven viability is utilized for transplantation. Seven consecutive patients with type 1 diabetes, with history of metabolic instability, who underwent this procedure, followed by glucocorticoid-free immunosuppressive regimen showed excellent metabolic control. Improved methods of transplantation are being carried out by encapsulation of the transplanted islets to minimize the need for immunosuppression.

KEY WORDS: Pancreatic islet transplantation: type 1 diabetes; Immunosuppression.

INTRODUCTION

Diabetes mellitus is the oldest known endocrine disorder to man. Prior to the introduction of insulin in 1922, ketoacidosis claimed the lives of 90% of diabetics within the first five years of diagnosis. Discovery of insulin in the year 1922 has significantly reduced the acute mortality rate due to this disease. However, the use of exogenous insulin has not prevented the secondary complications of this disease, particularly retinopathy, nephropathy, angiopathy and neuropathy, which collectively account for premature blindness, end stage renal disease, vascular disease and painful as well as disabling neuropathic disease.

USE OF EXOGENOUS INSULIN

Currently we have evidence to support the theory that keeping blood glucose levels under tight control, represents the most effective way either to prevent the onset or to reduce the progression of chronic microvascular complications of type 1 diabetes mellitus (1). At present, such a goal can only be accomplished by treating type 1 diabetics with intensified therapy regimens consisting of daily multiple insulin injections and this involves accurate blood glucose monitoring (2). Nevertheless, subcutaneously administered exogenous insulin, in spite of considerable improvement in both purity and pharmacokinetics of available preparations of insulin or its analogues (3) can never even approximate the pulsatile insulin secretory patterns of the normal islet β cell. Hence the development of an alternative approach for reaching and sustaining near-normoglycemia, as close as possible to the physiological model, would certainly improve the difficult task of circumventing or delaying the onset of unwanted sequelae of the basic disorder.

PANCREATIC ISLET TRANSPLANTATION

Transplantation of pancreatic islets represents a promising way for curing type 1 diabetes. It has been pursued in the past two decades with the goal of improving the quality of life of diabetic subjects and preventing the secondary complications of diabetes mellitus. Transplantation of islets that have been isolated from whole pancreas is an attractive alternative for the reversal of diabetes for several reasons. The islets comprise only 2% of the pancreas, and as only the islets are needed to reverse diabetes, it is logical to attempt to separate islets from the undesired exocrine tissue. A limitation has been the difficulty of isolation and purification of islets.

ADVANTAGES OF ISLET TRANSPLANTATION

An advantage of islet transplantation is that, the procedure is simple and safe. If islets are rejected, there is no need to re-operate to remove the graft. A further advantage in isolating purified islets relates to the problem of rejection. Although a whole pancreas is strongly immunogenic, the endocrine cells within the islet tissue are not. Thus, isolated islets afford the opportunity to alter immunogenicity of the tissue by deletion of resident immunocompetent cells without destroying the endocrine secretory cells (4).

Reversal of diabetes by transplantation of isolated islets was easy in rodents. The transition from successful animal studies to clinical trials has been more difficult than expected (5).

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Successful islet transplantation with documented normoglycemia in the absence of exogenous insulin therapy has been reported by some groups which is reflected in the International Islet Transplant Registry (6). This summary of adult islet allografts in patients with type 1diabetes reports on 294 graft performed by transplant groups throughout the world through December 1996. Data analysis has shown that 11% of the recipients were rendered insulin-independent for periods of more than 1 week, and at 1 year follow-up, 7% were insulin-independent.

LIMITATIONS OF ISLET TRANSPLANTATION

Failure of clinical islet transplantation is thought to be attributable to the following factors: non-functioning of isolated islets, the small number of transplanted islets, the immunogenecity of isolated islets, transplantation to inappropriate sites, recurrence of auto-immunity in the transplanted islets and rejection and immunosuppression. Of these factors, rejection is strongly suggested to be of major importance in limiting the clinical application of islet transplantation (7).

Current islet isolation and purification procedures presuppose that islet cell survival is independent of other elements of the pancreas, and that islets remain unaffected, in any fundamental way, by the conditions to which they are subjected. The peri-insular basement membrane, a component of the extra-cellular matrix, is a critical component of the pancreatic microenvironment that may be lost during the isolation process. Both disruptions of the cell-matrix relationship and the loss of basement membrane lead to the induction of apoptosis. In addition, islets are exposed to a variety of cellular stresses during isolation that elicit biochemical responses that either enhance cell survival or lead to cell death (8). There is still a large variance in the number, purity, viability and secretory capacity of islets isolated from brain - dead human donor pancreata and this significantly hampers the utilization of human islet preparations derived from a single donor for one diabetic recipient (9).

AIM OF ISLET TRANSPLANTATION

The aim of islet transplantation is to obtain normoglycemia and to improve the quality of life. The main benefit is to eliminate or minimize systemic complications like retinopathy and nephropathy. However, diabetic patients do not require a graft to ensure their survival like other patients who wait for a heart, liver, or lung transplantation. The diabetogenic effects of some immunosuppressive agents currently used and the increased incidence of infections and malignancies associated with chronic immunosuppression in long-term transplant recipients are well known, thus it is important to consider these possible adverse effects. For this reason, islets have usually been grafted in either simultaneous or deferred combination with kidney or liver in type 1 patients also suffering from end-stage renal or hepatic disease (10). Research is being carried out for immunomodulation, so that the islets are rendered less immunogenic.

IMPROVED METHOD OF ISLET TRANSPLANTATION

Improved survival of intra-portal pancreatic islet allografts in patients with type I diabetes mellitus by refined peritransplant management is reported. The principal features of the new protocol designed to overcome early graft failure are both technically and immunogenically related. They have used only highly purified islet preparations of proven viability; islets are cultured for 48-72 hours prior to transplantation, which may to certain extent, reduce the immunogenecity of the islets as demonstrated with rodent islets (11). Seven consecutive patients with type I diabetes mellitus and a history of severe hypoglycemia and metabolic instability underwent islet transplantation in conjunction with a glucocorticoid-free immunosuppressive regimen consisting of sirolimus, tacrolimus, and daclizumab. Islets were isolated by ductal perfusion with cold, purified collagenase, digested and purified in xenoprotein-free medium, and transplanted immediately by means of a peri-cutaneous trans-hepatic portal embolization. It has resulted in insulin independence with excellent metabolic control when glucocorticoid-free immunosuppression is combined with the infusion of an adequate islet mass (12). Continued insulin independence for up to 2¾ years is possible after islet transplantation. There are acute risks of the procedure and risks associated with the immunosuppressive drugs, demonstrating the need for further improvement (13).

Improved methods of isolation using different solutions are being attempted (14). Encapsulation circumvents the need for immunosuppression because the transplanted living cells are surrounded by a semi-permeable membrane which protects them the host's immune system. Alginate-poly-lysine spherical-bead microcapsules (with improved bio-compatibility, mechanical strength, and chemical stability) can now provide a large surface area, enhanced nutrition and oxygen supply, precisely tailored porosity (to discriminate nutrients from immunoglobulins), maximum protection from membrane failure, and direct

injectability into the peritoneal cavity. Therapeutic effectiveness of alginate-poly-lysine microcapsules for the transplantation of human-insulin producing cells into a human diabetic patient is reported (15). Islet transplantation experiment using non-human primates are being carried out (16).

CONCLUSION

Several problems continue to afflict islet transplantation, a strategy that has held such a great deal of promise for the cure of type 1 diabetes over the past three decades. In spite of scarce success so far, this scientific enterprise continues relentlessly to drain tremendous research efforts and resource expenditures (17).

REFERENCES

1. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993; 329: 976-86.

2. Fenelli CG, Epifano L, Rabotti AM, Pampnelli S, D Vincenzo A, Modarelli F, Lepore M, Amnibale B, Ciofetta M, Bottini P, Brunetti P, Bolli GB. Meticulous prevention of hypoglycemia normalizes the glycemic thresholds and magnitudes of most of neuroendocrine responses to symptoms of, and cognitive function during hypoglycemia in intensively treated patients with short-term diabetes. Diabetes 1993; 42: 1683 -9.

3. Torlone E, Fanelli C, Rambotti AM, Kassi G, Modarelli F, Di Vincenzo A, Epinfano L, Ciofetta M, Pampaneli S, Brunetti P, Bolli GB. Pharmacokinetics, pharmacodynamics and glucose counterregulation following subcutaneous injection of the monomeric insulin analogue. (Lys-B28, Pro B29) in IDDM. Diabetologia 1994; 37: 713-20.

4. Alejandro, R. Transplantation of islets of Langerhans in patients with insulin dependent diabetes mellitus. Scand.J. Gastroenterol. 1995; 208: 125-8.

5. Anderson, A., Jansson,L., Sandler,S., Korsgren, O., Sundler, F. Cell biology of the transplanted pancreatic islet: Impact of hyperglycaemia. Insulin secretion and pancreatic B-cell research. *Ed.* P.R. Flatt, S.Lenzen. 1994; Smith Gordon, U.K.

6. International Islet Transplant Registry Newsletter, December 1996; Vol.6, no.7.

7. Yamaski T, Inoue K, Hayashi H, Gu, Y Setoyma H, Id J, Cui W, Kawkami Y, Jogire M, Imamura M. Effect of a new immunosuppressive agent FTY720, on survival of islet allografts. Cell Transplantation 1998; 7: 403-6.

8. Rosenberg L, Wang R, Paraskevas S, Maysinger D. Structural and functional changes resulting from islet isolation lead to islet cell death. Surgery 1999; 126: 393 - 8.

9. Mahler R, Franke,F.E., Hering B.J, Brandhorst D, Brandhorst H, Brended M.D, Federlin K, Schulz A, Breatzel R.G. Evidence for a significant correlation of donor pancreas morphology and the yield of isolated purified human islets. J. Mol. Med. 1999; 77: 87-9.

10. Cretin N, Buhler U, Fournier B, Caufield A, Oberholzer J, Mentha G, Morel PH. Human islet allotransplantation: World experience and current status. Dig. Surg. , 1998; 15: 656-62.

11. Bretzel R.G, Brandhorst D, Brandhorst H, Eckhard M, Ernst W, Friemann, Rau W, Weimar B, Rauber K, Hering B.J, Brended M.D. Improved survival of intraportal pancreatic islet cell allografts in patients with type-1 diabetes mellitus by refined peritransplant management. J. Mol. Med. 1999; 77: 140 -3.

12. Sharpio A.M.J, Lakey J.R.T, Ryan A.E, Korbutt G.S, Toth E, Warnock G.L, Kneteman N.M, Rajotte V.R. Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free Immunosuppressive regimen. N. Engl J Med. 2000; 343: 230 -8.

13. Ryan E.R, Lakey J.R.T, Paty B.W, Imes S, Korbutt G.S, Kneteman N.M, Bigam D, Rajotte V.R, Sharpio A.M.J. Successful islet transplantation. Continued insulin reserve provides long-term glycemic control. Diabetes 2002; 51: 2148-57.

14. Kenmochi T, Myomota M, Saski h, Une S, Nakagawa Y, Moldvan S, Benhamou P.SY, Brunicardi F.C, Tanaka H, Mullen Y. LAP-1 Cold preservation solution for isolation of high-quality human pancreatic islets. Pancreas 1998; 17: 367-77.

15. Soon-Shiong P. Treatment of type I diabetes using encapsulated islets. Advanced Drug Delivery Review 1999; 35: 259- 70.

16. Kenyon N.S, Fernandez L.A, Lehmnn R, Masettin M, Ranuncoli A, Chatzipetron M, Iaria G, Han D, Wagner J.L, Ruiz P, Berho M, Inverardi L, Alejandro R, Mintz D.H, Kirk A.D, Harlan D.M., Burkly L.C., Ricordi C. Long-term survival and function of intrahepatic islet allografts in baboons treated with humanized anti-CD154. Diabetes 1999; 48: 1473 - 81.

17. Calafiore R. Perspective in pancreatic and islet cell transplantation for the therapy of IDDM. Diabetes Care 1997; 20: 889 - 96.