HISTORY AND CONCEPT OF ISLET CELL TRANSPLANTATION

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Abstract

Diabetes Mellitus is a chronic disease characterized by a conglomeration of metabolic disturbance of carbohydrate and fat metabolism. Since its recognition around 1500BC, its management was always a challenge for practitioners and has gone through a series of milestones starting with the introduction and use of Insulin in 1921; an established standard for treating Type I diabetes, followed by the introduction of Pancreatic transplantation which was firstly performed in 1966, culminating with the era of Islet cell transplantation which has propagated to a promising pace since 1972. The Edmonton protocol of Islet cell transplantation, which was introduced by Shapiro et al in 2000, adopts an innovative use of immunosuppression drugs with fewer side effects. This paper outlines the historical propagation of treating type 1 diabetes. It highlights the advent of using islet cell transplantation as a newer noninvasive means of providing persistently endogenous insulin for type 1 diabetic patients. This is considered a better accepted way of restoring euglycemia with the merit of avoiding attacks of hypoglycemia which is a well-known side effect of Insulin therapy. Once a dream, islet cell transplantation for treatment of diabetic patients was never as close to being a reality as it is today. We can now see the light at the end of the tunnel through the dramatic discoveries including newer technologies to overcome the prolonged need for immunosuppression, the use of encapsulated islet xenografts, the generation of the unlimited supply of human β cells, and the use of embryonic and adult stem cell.

Keywords: islets of Langerhans, Diabetes, History of Medicine
Introduction

Diabetes Mellitus (DM) is a historical disease that drew the attention of humanity since its recognition around 1500 BC by ancient Egyptians, describing a rare disease in which a person urinates excessively & losses weight. It was not until 1600 years later that the Greek physician Aretaeus, recognized that the urine of the affected persons has a sweet taste, coining it for the first time as Diabetes (Poretsky 2009). According to the World Health Organization (WHO), 347 million people worldwide have diabetes and it is the cause of mortality of 3.4 million every year (Danaei 2011, WHO 2009). WHO further predicts that deaths from Diabetes would double between 2005 and 2030 (WHO 2013). A formerly labeled rare disease is now announced as a global pandemic posing a challenge to public health agencies worldwide.

Diabetes is a complex heterogeneous disorder characterized by hyperglycaemia caused by a total lack, decrease or diminished effectiveness of circulating insulin. Genetically both Type 1 (T1D) and type 2 diabetes (T2D) are polygenic disorders, and multiple genes and environmental factors contribute to the development of the disease (Ounissi-Benalha 2008, Stolerman 2009).

T1D occurs predominantly in children and young people and is due to selective auto immune destruction of β cells leading to absolute insulin deficiency (Mathis 2001). On the other hand patients with T2D have a strong family history of T2D, more so than in T1D. Type 2 Diabetes mostly affects older people who consume high calorie diet and with relatively sedentary life style leading to a state of cellular insulin unresponsiveness (Insulin resistance) resulting in increase of pancreatic insulin secretion. The resultant β cell exhaustion necessitates the need of exogenous insulin in the patients’ therapeutic regimen (Costa 2002). T1D affects millions of individuals and is associated with multiple medical problems due to the relatively longer life span of the affected persons. Premature atherosclerosis is a cause of substantial morbidity and mortality in T1D and tight control of glycemia was found to reduce the risk of developing cardiovascular disease (Costacou 2007, Nathen 2005). However, intensive insulin treatment is associated with three fold increase in severe hypoglycemia an obstacle in attempts to attain good glycemic control (DCCT 1993).
Pancreatic Islet Cells

Identified in 1869 by Paul Langerhans, the islets are the endocrine cells of the pancreas which secrete their hormones directly to the blood (Langerhans 1869). The islets constitute 1-2% of the mass of the pancreas. A healthy adult pancreas contains about one million islets, each islet measuring 0.2 mm in diameter, with a combined mass of the islets of 1 to 1.5 grams (Sleisenger 2009). Islets are distributed among the exocrine tissue of the organ. Each islet is surrounded by thin fibrous connective tissue capsule which is intermingled with the connective tissue of the pancreas. In humans four main cell types are found within the islets; α cells secreting glucagon, β cells secreting Insulin, δ cells secreting somatostatin and γ cells secreting pancreatic polypeptide. Within the islet architecture, human islets display alpha and beta cells in close relationship with each other throughout the cluster (Brissova 2005, Cabrera 2006). The clusters of the islets are embedded in a network of capillaries. The flow of blood in this glomerular-like vasculature is regulated by signals, such as nutrients and hormones from remote tissues. Islets have a portal circulation, with blood flowing from beta to alpha to delta cells (Samols 1988). In addition, islet perfusion determines communication between endocrine and exocrine cells (Ballian 2007).

Implementation of Insulin Therapy in Type 1 Diabetes

Insulin therapy is the gold standard for treating people with T1D. The rationale of intensive treatment of type 1 diabetes was introduced after the establishment of the modern standard of care for the medical management of type 1 Diabetes Mellitus by the Diabetes Control and Complications Trial (DCCT) in 1993 and its follow up study; Epidemiology of Diabetes Interventions and Complications (EDIC) (Nathan 2005, DCCT 1993). After assigning 1441 patients to either conventional or intensive treatment (by applying multiple daily measurements of blood glucose levels with the combination of daily insulin injections of long, intermediate & short acting insulin in addition to dietary and psychological support) the study showed better glycemic control and less secondary complication rates in the intensive treatment group than in the conventional group, rendering the intensive treatment an accepted norm in Diabetes management. Despite better microvascular outcomes, intensive insulin therapy was hindered by a high rate of frequent and severe hypoglycemia (62 episodes per 100 patient-years of therapy).
Rationale for Insulin Producing β Cells Transplantation

The restoration of β- cell mass and reversing diabetes was the reverie of scientists since the recognition of the role of pancreas in treating diabetes. Logically, this needs to be accomplished by two approaches; either by endogenous regeneration of β cells or by transplantation of β cells from exogenous sources. Advances in both approaches are promising. Regeneration of β cells from embryonic and adult stem cells or pancreatic progenitor cells is work in progress that is beyond the scope of this review (Bonner-Weir 2005).

Transplantation of Insulin producing β cells was performed earlier as a vascular procedure by transplanting the whole pancreas (The world first clinical pancreas transplant was performed at the University of Minnesota in 1966 to treat a uremic diabetic patient) (Kelly 1967) . This approach proved to be a cost effective option that offers independence from exogenous insulin, with favorable glucose levels. The procedure proved to ameliorate the complications of DM and improve the quality of life and patients’ life expectancy (Fioretto 1998, Navarro 1997). Since that time more than 15000 pancreas transplants has been performed around the World with 85% one year graft survival rate, and with insulin independent recipient (Sutherland 2001) . The DCCT provided a strong ground for using pancreatic transplantation. It provided evidence that simultaneous kidney and pancreas transplantation is the treatment of choice for most diabetic people with end stage renal failure with a 3- year survival rate of approximately 70- 80 % , simulating the rates for most of other organ transplantation (Gruessner 2001) . Kidney biopsies had shown dramatic reversal of the mesangial accumulation and basement membrane thickening 10 years after the establishment of normal glycemia following pancreas transplantation. Of note is that macrovascular complications as well as the sensory, motor and autonomic neuropathy were stabilized (Fioretto 1998, Fiorina 2001).

Historical Aspects of Islet Transplantation

1. Pancreas Transplantation

The concept of transplanting extracts or pieces from the pancreas to patients with diabetes dates back to 1894 when Williams used minced sheep’s pancreas for oral and subcutaneous therapy. This adventurous trial proved a failure, presumably due to using xenografts without immunosuppression (Williams 1894).
It was not until 1972 that a successful trial by Ballinger and Lacy of transplanting isografts from normal rats to streptozocin induced diabetic rats could reverse diabetes (Ballinger 1970).

Islets autografts were transplanted successfully in 1980. This was performed on a patient with painful chronic pancreatitis in whom the pancreas was removed, minced, digested with collagenase and unpurified preparation of islets was re-infused into the patient portal vein. Being large in size the islets lodged in the liver without reaching the sinusoids (Sutherland 1980). In the 1990s, some promising reports were documented, with some recipients showing insulin independence for up to one year after the procedure. Wahoff et al. reported insulin independence rate of 74% two years after autologous islet transplantation in 14 patients receiving portal vein infusion of islet cell extracts from their removed pancreas (Wahoff 1995). Trials during the years 1990 to 1995 showed success in only 6 percent of the islet transplants (Hering 1996). The Islet Transplant Registry records of 267 patients who had undergone islet allograft transplantation showed that 12.4% of patients were insulin independent for 7 days. Only 8.2% of them stayed independent for one year (Brendel 1999). It is worth mentioning that these early trials adopted an immunosuppression protocol using anti-lymphocyte globulin combined with Cyclosporine, azathioprine and corticosteroids. The use of immunosuppression in transplantation procedures is a considerably challenging issue due to the balance sought between their efficacy and their toxicity to the islet cells. These drugs are diabetogenic as they were found to increase the peripheral insulin resistance. In addition, they have an antiproliferative effect on the engrafted tissue (Ishizuka 1993, Hyder 2005, Lohmann 2000). The high concentration of these drugs in the liver imposes more risk to the engrafted islets at their site of lodgment in the liver sinusoids.

2. **Islet Cell Transplantation**

Despite the improvement in insulin therapy in treating T1D, many patients are disabled by the refractory hypoglycemia. Compared to pancreas transplantation, introducing cell-based therapy by transplanting islet cells provides minimally invasive means to restoring euglycemia with the avoidance of the complications of surgical procedures. Islet cell transplantation underwent a substantial progress during the last three decades (Hering
1999, Ricordi 2004). Few centers performing the procedure have shown high rates of favorable insulin independence in patients with T1D.

The use of newer immunosuppressive agents was introduced in 2000 at University of Alberta, Edmonton by Shapiro et al who developed a corticosteroid-free immunosuppressive protocol that includes Sirolimus, low dose tacrolimus and a monoclonal antibody against interleukin-2 receptor (Daclizumab) for use in trial of islet transplantation in patients with brittle T1D (Shapiro 2000).

The trial reported 100% success rate of restoring normal glycaemia in seven patients during a median follow up of 11.9 months. This was achieved by applying more rigorous criteria to attain sufficient mass of transplanted islets to achieve normal glucose levels. The new approach resulted in sustained freedom from the need for exogenous insulin with better outcome when compared to previous reports (Brendel 1999). However, five years later the results of Edmonton Protocol showed some discouraging trends. Only 15% of the patients were free of exogenous insulin treatment although 85% still showed evidence for the presence of plasma C-peptide which is an indication of endogenous insulin secretion by the transplanted islets (Shapiro 2005).

An international multicenter trial of the Edmonton Protocol was conducted to explore the feasibility of islet transplantation with the use of the Edmonton protocol (Shapiro 2006). Thirty-six subjects with T1D were recruited from 9 centers. The islets were obtained from pancreata of deceased donors and transplanted within two hours after purification. The primary end point was insulin independence one year after the final transplant. Of the 36 recipients, 44% met the primary endpoint (Hemoglobin A1c < 6.5; Fasting blood sugar < 140 mg/dl; Post prandial sugar < 180 mg/dl). Twenty eight percent had partial function of islets (C-peptide > 0.3 ng/ml). Twenty eight percent had graft loss one year after the final transplantation and 58% had insulin independence at any point throughout the study. The multicenter study confirmed the former experience with the single center Edmonton protocol and demonstrated the benefit of islet transplantation in patients with brittle T1D. It proved that even in patients with residual islet function, severe hypoglycemic episodes were minimized. The trial also standardized pancreas selection, recipient selection, islet processing and post transplantation care.
**Indications of Islet Transplantation:**

1. Autologous Islet Transplantation in pancreatectomy-induced diabetes, if the pancreas is affected by trauma, chronic pancreatitis or benign neoplasms.

2. Allogenic Islet Transplantation is indicated in T1D as Islet transplantation alone (ITA), Simultaneous islet and kidney transplantation (SIK) and as Islet after kidney transplantation (IAK) (Pileggi 2004).

3. Allogenic transplantation is indicated in patients with diabetes having other metabolic disorders like cystic fibrosis and hemochromatosis (Lanng 1992).

4. Other rare indication is in people with T2D and liver cirrhosis, although advanced patient’s age and comorbidity are contraindications to this procedure (Ricordi 1997).

**Islet Transplantation Technology:**

The modern islets isolation technology includes:

1. Procurement of healthy pancreas from brain dead donor whose heart is beating. Recently cadaveric donors are being used successfully.

2. Cannulation of the pancreatic duct, collagenase infusion to dissociate islets from exocrine, ductal and surrounding connective tissues.

3. Distended pancreas is cut into smaller pieces and transferred into so-called Ricordi’s chamber, where digestion takes place to liberate and remove the islets from solution. (A recipient needs more than 12,000 islet equivalents/kg; IE, the number of islets normalized to an islet of 150 μm of diameter). Around 5000 IE/kg can be obtained from one pancreas. Islet isolation may cost around $10,000 US)

4. Purification of the islets from the enzyme by centrifugation, to minimize the volume of the tissue to be implanted by separating the exocrine tissue and debris, hence decreasing the insult to the liver to prevent portal hypertension.

5. Transplantation; either immediately or after culturing for a short time to assure sterility and to assess in vitro the function of islet preparation. In addition, culturing helps in
modulating the islets regarding immunogenicity and induction of cyto-protective molecules, and genetic modification of the islets before transplantation.

These strategies were required to reduce the coagulation/ complement activation and inflammation which may cause islet tissue rejection by the recipient (Villiger 2005). Culturing also helps in preconditioning the recipient regarding immune suppression and reduction of inflammation (Pileggi 2006).

6. Islet infusion to the recipient under conscious sedation, using ultrasonic or fluoroscopic guidance. Islet cells infused though a needle introduced via the skin into the right portal vein. The implants are then engrafted into the liver sinusoids and are ready to function. The islet infusion can be repeated on several occasions to deliver the appropriate amount of islets to achieve the optimal glycemia (Robertson 2004).

7. Other sites for infusion are the kidney capsule, spleen, testes, peritoneal cavity, small bowel, intramuscularly, and subcutaneously.

8. The situation after the infusion may not be favorable and many islets fail to engraft and function. This can be attributed to the prolonged hypoxia during the revascularization period which may take about two weeks. In addition the risk of bleeding when anticoagulation or antiplatelet drugs are used during the infusion as well as the blood mediated inflammatory reaction secreting inflammatory cytokines by the recipient lymphocytes which contribute to apoptosis and necrosis of the newly harbored β cells. The process of rejection peaks in two to three days and ends by two weeks (Hyder 2005). Another challenge that might affect the function and viability of the engrafted islets is the antiproliferative effect of immunosuppressive drugs which hinders angiogenesis for the newly transplanted islets.

**Clinical Effect of Islet Cell Transplantation**

Few papers discuss the clinical effects of islet transplantation on type 1 diabetic patients regarding morbidity and mortality. One paper studied the effect of islet transplantation on patients’ survival. Comparing two groups who had kidney islet transplant; one group showed C peptide secretion > 0.5ng/ ml and the other lost C peptide with early failure of the engrafted tissue. After seven years of follow up, the successful group with sustained restoration of β
cell function had significantly higher survival rate (90%) than the other unsuccessful group (51%).

The higher survival in the successful group was accompanied by higher C-peptide levels and lower insulin requirement compared to the unsuccessful group, despite similar glycated hemoglobin levels. The cardiovascular deaths were higher in the latter group with poorer atherosclerotic profile and endothelial function (Fiorina 2005)

**Effect of Islet Transplantation on Long Term Diabetes Complications**

No controlled studies have addressed the question whether Islet transplantation can halt or delay chronic diabetic complications. This is attributed to the difficulty of performing large clinical trials in the lack of standardized protocols, the variable methods of isolation of the islet tissue and the use of different immunosuppressive measures.

Animal studies had shown that Islet transplantation can improve cases of diabetic cardiomyopathy. An uncontrolled study on a small number of patients showed improvement in cardiovascular function over 3 years follow up period in kidney transplant recipient with functioning islet transplants (Laviola 2001).

One of the results of this study was the delay in intima medial thickening and improvement in atrial and ventricular function.

Nephropathy is one of the most common chronic complications of T1D (DCCT 1993). DCCT demonstrated a reduced incidence of microalbuminuria in type 1 diabetic patients in the intensive group compared to the conventional group. A paper published in 2003 showed that successful islet transplantation in T1 diabetic patients with end stage kidney disease receiving kidney transplant had prolonged graft survival and prevent reduction in vascular function of the graft (Fioina 2003). Better renal vascular function was demonstrated in another group of patients with kidney transplant and functioning islet transplant compared to the group without functioning islets (Fiorina 2005).

Diabetic retinopathy is a well-recognized complication of diabetes (DCCT 1993). It is characterized by new vessel formation and reduced retinal blood flow, hypoxia and distorted endothelial integrity (Miller 1997). A recent case control study on 10 patients who received islet transplantation alone compared with a control group of type 1 diabetic patients used a
color-Doppler-imaging to study the effect of ITA after one year on the blood flow velocities of central retinal artery and vein.

A statistically significant increase of blood flow velocities of central retinal arteries and veins was found only in the ITA patients (Frank 2006). An early, significant increase of arterial and venous retinal blood flow velocities was found after ITA.

Peripheral nerve function was assessed with a nerve conduction velocity (NCV) index in islet transplanted patients in a 2 years follow up study. There appeared to be a positive effect of β cell implantation on polyneuropathy. This study did not provide a statistical analysis (Lee 2005). Another report indicated that islet transplantation can induce long lasting stabilization or even improvement of poly neuropathy in type 1 kidney transplanted diabetic patients who received functioning islet transplant (Del Carro 2007).

Conclusion

Islet transplantation is an evolving therapeutic measure for highly selective patients with severe hypoglycemia or labile T1D. It remains at cross roads due to the critical shortage of donor organs, the poor long term results, and the relatively high incidence of adverse effects as well as its high cost. Therefore the procedure is still unsuitable to be expanded to the general population.

Nonetheless the dramatic discoveries and the expansion of the horizon to include newer technologies which overcome the issue of prolonged need for immunosuppression by using encapsulated islet xenografts, generating an unlimited supply of human β cells, and the use of embryonic and adult stem cell, set the stage for a dream come true in transplanting islets cells to treat diabetic patients.

Conflict of Interest: The author reports no conflict of interest.

The work is original and had not been published or submitted elsewhere.
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