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Overview of Islet Cell Transplantation

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Introduction

Globally, diabetes affects over 382 million people, with roughly 10% presenting with type 1 DM (T1DM) and is predicted to rise to 592 million by 2035.1 An annual 3% rate of growth affords an escalating financial burden where the International Diabetes Federation estimates in Canada alone diabetes-related health care costs was $14 billion in 2015. These are expected to climb to a staggering $16 billion once a year by 2020. Although the etiology of T1DM is incompletely elucidated, it's characterized as a multifactorial autoimmune disorder resulting from specific immune-mediated destruction of pancreatic beta (β) cells within the islets of Langerhans. Classic symptoms include polyuria, polydipsia, and polyphagia with confirmation of diagnosis marked by hyperglycemia, low or indetectible serum C-peptide levels, elevated glycosylated hemoglobin (HbA1c), and one or more positive autoantibody markers. Those with T1DM must administer frequent exogenous insulin therapy to take care of normoglycemia. Continuous glucose monitoring systems (CGM) and insulin pumps may further help mitigate glycemic fluctuation. Recently, the FDA approved a closed-loop technology that infuses glucose regulatory hormones (insulin and glucagon) in response to glycemic fluctuations. While tighter glycemic control with medical intervention has been clearly shown to scale back secondary complications, it substantially increases risk of severe hypoglycemic reactions. T1DM is related to a shortened anticipation by 13 years.

In consequence, the research community has focused on new avenues to arrest T1DM at the time of diagnosis. Intensive "new-onset" pilot trials conducted by Trial Net, a gaggle of researchers aimed toward identifying the prognosis and prevention of T1DM, have demonstrated means to sustained honeymoon periods and delayed diabetes onset. In Brazil, Voltarelli and colleagues are currently conducting clinical trials aimed to reset the system in new-onset diabetes through administration of peripheral blood autologous bone marrow-derived hematopoietic stem cells including immunodepleting conditioning (NCT00315133). This approach led to impressive reversal within the diabetic state in 21 children and adolescents with new-onset T1DM, but was also related to substantial side-effects. To date, no protocol has yet to eradicate exogenous insulin therapy entirely without substantial recipient risk. The growing prevalence of T1DM is concerning, and alternatives to insulin injections are needed desperately.

Beta cell replacement therapy through islet transplantation (IT) provides a possible alternative to exogenous insulin. The history of IT extends 23 years before the invention of insulin, when Watson-Williams and Harsant in 1893 in Bristol UK attempted to treat a 13 year old boy dying from acute ketoacidosis with transplantation of pieces of sheep's pancreas. Although the patient had minor glycemic improvements, he ultimately died 3 days after this futile first attempt at xenotransplantion. The concept of isolating islets wasn't revisited till 1972, when Paul E. Lacy restored glycemic control with intraportal vein infusion of islets into chemically-induced diabetic rats. In 1980, David Sutherland and John Najarian, two innovative surgeons working in Minnesota, demonstrated successful intraportal islet transplantation in 10 patients with surgical induced diabetes, where the patients' own islets (autografts) were infused back after islet isolation; ultimately 3 of those patients achieved insulin independence for 1, 9 and 38 months, respectively. the event of the Ricordi® Chamber and therefore the semi-automated method for islet isolation was developed by Camillo Ricordi while working in Paul Lacy's laboratory in St. Louis. This semi-automated method remains state-of-the-art today, and is out there commercially (BioRep, Miami, FL, USA). In 1990 David Scharp, also working with Camillo Ricordi and Paul Lacy in St. Louis, reported the primary case of transient insulin independence after islet allotransplantation, within the context of recipient immunosuppression. Despite substantial advances, fewer than 8% of the 267 islet transplant attempts between 1980 and 1999 resulted in insulin independence for extended than one year. In 2000, the Edmonton protocol developed by Shapiro et al. made IT a feasible clinical procedure. The Edmonton protocol was ground-breaking because it utilized a corticosteroid-free immunosuppressive protocol by combining two potent immunosuppressants: sirolimus and tacrolimus, along side an anti-CD25 antibody to guard against rejection and recurrent autoimmunity. This protocol augmented the islet mass with two or more fresh islet preparations, infusing a complete islet dose that was substantially above had been used previously in clinical islet trials (>13,000 islet equivalents (IE) kg−1 recipient body weight).16 All seven-consecutive treated T1DM subjects remained insulin independent for >1 year with sustained C-peptide production after hepatic portal vein infusion. A subsequent 5-year follow of the Edmonton protocol demonstrated that the majority subjects lost complete insulin independence by year 3–5, with only 10% remaining insulin free by 5 years. However 80% maintained strong C-peptide secretion, which was sufficient to correct the HbA1C.

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