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A Review Article on the Emerging Role of Islet Cell Transplantation in Type 1 Diabetes Mellitus

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Abstract:- The metabolic disease known as juvenile diabetes, or Type 1 diabetes is characterized by a reduction in insulin production, which is vital for an individual's survival. Islet-cell-transplantation is an experimental approach of transferring pancreatic islet cells from donor pancreas to a suitable diabetic patient. Upon implantation the islets begin to produce insulin that is sufficient to maintain blood glucose levels. In this review we discuss what is currently known about pancreatic islet transplantation, its risks and benefits. Based on current evidence, pancreatic islet transplantation appears to be an experimental surgery that is demonstrating promising outcomes for the patients. However, islet transplantation have not been studied comprehensively enough to introduce it as a routine procedure.

I. INTRODUCTION

Type 1 diabetes mellitus is an persistent endocrine illness that is primarily caused by reduced pancreatic insulin production as a result of beta cell destruction brought on either by idiopathic or autoimmune T-cell mediated means. The onset of symptoms are usually below the age of 30. [1] Islet cells especially beta type regulates and maintains blood glucose and insulin levels in our body. [2] The activation of T-helper cells by autoantigens results in the release of cytokines, which inflame and ultimately kill beta cells.[3] The symptoms included are nausea, vomiting, dehydration, weight loss, polyuria, polydipsia, blurred vision, and fatigue, slow healing of cuts and sores, drowsiness, shortness of breath, diabetic ketoacidosis. Type 1 diabetes is diagnosed by the following tests- Blood glucose test (RBS, FBS, PPBS), HbA_{1C}, Glucose tolerance test, Antibody test, Urinalysis. The current pharmacological treatment uses for type 1 diabetes is Insulin therapy throughout the life, the insulin preparations include NPH, regular human insulin, insulin lispro, insulin aspart. The maintenance dose of insulin is 0.5-2 units/kg/day and it may vary depending on the patient's condition. [4]

A medical experiment known as "Islet cells transplantation" involves transferring healthy beta cells from the donor to the recipient in lieu of the damaged islet cells. This can only be carried out in clinical trials that have FDA approval in the United States. [5] A qualified medical professional is required to test, purify, process and transfer the cells to the recipient after removing them from the donor. [6] After receiving an islet cell transplant, more than 70% of individuals with type 1 diabetes have been insulin-independent for years. [7]

II. ELIGIBILITY

People with type 1 diabetes who are between the ages of 18 and 65 are usually considered candidates for islet cell transplantation. They frequently experience moments of unconsciousness due to a shortage of insulin, and they typically exhibit early indicators of renal problems that might later result in kidney failure. [8]

Physicians choose candidates for islet transplantation based on whether the potential advantages outweigh the dangers, which include the potential for immunosuppressant side effects, and include things like improved blood glucose control without the need for issues like hypoglycemia. Immunosuppressive medications are necessary for recipients to prevent their immune system from attacking the islets they received during transplantation. An islet transplant may be a possibility for those with type 1 diabetes who intend to get a kidney transplant in order to address renal failure. Islet transplantation can be carried out concurrently with kidney transplant with kidney transplantation or following one. Immunosuppressants are already administered to kidney transplant recipients in order to prevent rejection from the donated kidney. [5]

III. PROCEDURE

For islet transplantation, the pancreas of a deceased organ donor is used to harvest islets. After being cleaned and processed, the islets are placed into the recipient's vein, which leads to liver. Nowadays, transplantation is most often performed on the liver due to its low thrombosis rates and less invasive nature.[9] The islets from a donor's pancreas are extracted using specialized enzymes. Islets cells are delicate, thus transplant takes place right away after they are removed. Radiologists frequently conduct islet transplants. They use x-ray and ultrasonography images to direct the placement of a catheter into the upper abdominal portal vein. The liver is then gradually infused with islets via the catheter. As soon as

the islets are transplanted, their beta cells begin to synthesize and release insulin. After an islet transplant, people with type 1 diabetes might not require daily insulin injections. A patient with diabetes may get about 10,000 islets equivalents per kilogram of body weight from two donor pancreas. It sometimes takes two transplants for a person to become insulin independent. Less islet equivalents from a single donor pancreas may be needed for some individuals. [10] [11]

IV. RISKS OF ISLET TRANSPLANTATION

Stable blood sugar regulation is made possible by pancreatic islet transplantation. Type 1 diabetic patients are free from repeated severe hypoglycemia and become insulin-independent. However, bleeding may occur at the puncture site in the liver. Portal vein thrombosis is also a possibility. Risks are involved with the chronic use of immunosuppression drugs. [7] [12]

There are several complications associated with immunosuppressant's, including the patient's stomatitis. And other common symptoms include episodic diarrhea after treatment with GCSF, swelling of the legs due to fluid retention (leg edema), general malaise, and severe neutropenia (an absolute neutrophil count <500/mm3). There are side effects. During the immunosuppression stage, there is a risk of invasive infections such as urinary tract infections, skin infections, and pneumonia. [13] [14]

When human pancreatic islets transplanted from another person, antibodies may produce against proteins (antigens) in the islet tissue. The antibodies create memories for these antigens and mark them for destruction. This reminder can make it difficult to undergo another transplant at a later date because the next time the immune system recognizes these antigens, the immune response will occur much faster. That would make kidney or other organ transplants less likely to be successful. [15]

V. BENEFITS OF ISLET TRANSPLANTATION

For beneficiaries of islets, there are advantages in addition to their drawbacks. Enhanced blood sugar levels, fewer or no incidences of severe hypoglycemia episodes, decreased or eliminated insulin injection requirements for diabetes management and more awareness of hypoglycemia to help avert hypoglycemia episodes are few of these. Along with benefits, scientists believe that islet transplants could stop or postpone the development of diabetes consequences such as kidney disease, heart disease, nerve and eye damage.[16]

Usually, in response to hypoglycemia, endogenous insulin secretion stopped, glucagon secretion is activated. In order to stop or control the course of the disease in hypoglycemia, this causes a decrease in the ratio of insulin to glucagon exposed to the liver, increasing endogenous glucose production. [17] [18]

VI. RESULT

Phase 3 clinical trial, funded by the National Institute of Health (NIH), carried out by the Clinical Islet Transplantation Consortium External link which tests new treatments in large population to monitor the side effects and effectiveness of the treatment. According to the research, after more than a year from the treatment, 50% of the patients didn't require insulin, and nine out of ten had $HbA_{1C} < 7\%$ and no severe hypoglycemia episodes. Seven out of ten transplant recipients had $HbA_{1C} < 7\%$ two years after the procedure, no bouts of severe hypoglycemia occurred, and 40% of recipients didn't need to take insulin. The study's findings also indicate that the beneficiaries' quality of life in regard to their diabetes significantly improved.[19]

According to the data from The Collaborative Islet Transplant Registry in 2020, 50% of type 1 diabetic patients are free of insulin administration at one year, 30% of the patients at three years and 30% of the patients at five years. [8]

VII. CONCLUSION

Transplanting islets is not a usual pharmacotherapy used to treat type 1 diabetes. All over the world it is still considered as an experimental procedure. Despite the promising results of this experimental procedure, there are liabilities involved. In addition, there are not enough donors available, thus it is not a common surgical procedure yet. This treatment option still has to be improved through advancements in research, but this research could help make the surgery more readily accessible to patients with type 1 diabetes in the future. The key objective of every islet cells transplantation is to remove the possible risk of rejection and reduce the requirement of immunosuppressives. The focus of current islet transplantation research for diabetes treatment is on the microenvironment of the transplanted locations, including tissue-resident immune cells, extracellular matrix composition, and vascularization. The transplanting locations are unable to support the islets cells' long term survival. Whether aging and other physiological health problems have an impact on the longevity of transplanted islets is still up for debate. A growing body of research is increasingly concentrating on the development of customized hydrogel-based materials and macro devices to generate a transplantation space, safeguard the graft from the immune system and promote angiogenesis.

REFERENCES

[1]. Elizabeth A. Hackett and Stephan N. J. Jackson, Fifth edition(2012), Clinical Pharmacy and Therapeutics by Roger Walker and Cate Whittlesea, Elsevier.
[2]. Kenneth L Brayman, MD, Islet Cell Transplantation, UVAHealth, Sept 2017. https://uvahealth.com/services/islet-cell
[3]. Shaishavi Jansari, Nayan Devashri, Ankita Dhanani, Neelam Chauhan, Differentiation of stem cells into pancreatic beta-cells: regenerative medicine for diabetes, Shaishavi Jansari. Et al. / International Journal of Biological & Pharmaceutical Research, October 2014; 5(12): 901-909.

https://www.researchgate.net/figure/A-schematic-diagram-for-pathogenesis-of-Type-1-Diabetes-Mellitus_fig1_267514394
[4]. Cleveland clinic, https://my.clevelandclinic.org/health/diseases/21500-type-1-diabetes
[5]. National Institute of Diabetes and Digestive and Kidney Diseases, Pancreatic Islet Transplantation. https://www.niddk.nih.gov/health-information/diabetes/overview/insulin-medicines-treatments/pancreatic-islet-transplantation
[6]. Carolyn Farnsworth, What to know about islet cell transplants, MedicalNewsToday, January 31, 2022. https://www.medicalnewstoday.com/articles/islet-cell-transplant#islet-cell-transplant
[7]. Shinichi Matsumoto, Islet Cell Transplantation for Type 1 diabetes, 8PubMed, 2010 Mar;2(1):16-12. doi: 10.1111/j.1753-0407.2009.00048.x. EPUB 209 Aug 17. https://pubmed.ncbi.nlm.nih.gov/20923470/
[8]. Michael Dansinger, MD, Islet Cell Transplantation for the Treatment of Diabetes, WebMD, September 09, 2023. https://www.webmd.com/diabetes/islet-cell-transplantation
[9]. Fritz Cayabyab, Lina R. Nih, Eiji Yoshihara, Advances in Pancreatic Islet Transplantation Sites for the Treatment of Diabetes, Front. Endocrinol., 13 September 2021 Sec. Diabetes: Molecular Mechanisms Volume 12–2021| https://doi.org/10.3389/fendo.2021.732431
[10]. James M. Gardner, M.D., Ph.D.; Andrew M. Posselt, M.D., Ph.D.; Peter G. Stock, M.D., Ph.D.; Shareef Syed, MBChB, MRCS; Islet Transplantation for Type 1 Diabetes, Transplant Surgery, UCSF, 2023. https://transplantsurgery.ucsf.edu/conditions--procedures/islet-transplant-for-type-1-diabetes.aspx
[11]. Martin Hertl, MD, PhD, Pancreatic Islet cell Transplantation, MSD Manuals, Sept 2022. https://www.msdmanuals.com/en-in/home/immune-disorders/transplantation/pancreatic-islet-cell-transplantation
[12]. Gianna Melillo, Dr. Camillo Ricordi Outlines the Risks of Islet Transplantation for T1D, American Journal of Managed Care, Sept 20, 2021. https://www.ajmc.com/view/dr-camillo-ricordi-outlines-the-risks-of-islet-transplantation-for-t1d
[13]. Boaz Hirshberg, MD; Kristina I. Rother, MD; Benicio J. Diagon, IIII, MD; Janet Lee, MD; Jason L. Gaglia, MD; Richard Chang, MD; Bradford J. Wood, MD; David M. Harlan, MD, Benefits and risks of Solitary Islet Transplantation for Type 1 Diabetes Using Steroid-Sparing Immunosuppression: The National Institute of Health experience, Diabetes Care 2003;26(12):3288-3295 https://doi.org/10.2337/diacare.26.12.3288
[14]. Edmond A. Ryan; Jonathan R.T. Lakey; Breakup W. Paty; Sharleen Imes; Gregory S Korbutt; Norman M. Kneteman; David Bigam; Ray V. Rajotte; A.M. James Shapiro. Successful Islet Transplantation: Continued Insulin Reserve Provides Long-Term Glycemic control, Diabetes 2002;51(7):2148-2157, https://doi.org/10.2337/diabetes.51.7.2148.
[15]. Ryan EA, Paty BW, Senior PA, Shapiro AMJ. **Risks and Side Effects of Islet Transplantation.** *Curr Diab Rep 2004***; 4:304**-309.**PubMed**
[16]. Shapiro AM, Pokrywczynska M, Ricordi C. Clinical pancreatic islet transplantation. Nature Reviews. Endocrinology. 2017;13(5):268-277.
[17]. Michael R Rickels, R Paul Robertson, Pancreatic Islet Transplantation in Humans: Recent process and Future Directions, Endocrine Reviews, Volume 40, Issue 2 April 2019, Pages 632-668, published : 12 December 2018, https://doi.org/10.1210/er.2018-00154
[18]. Rickels MR, Fuller C, Dalton-Bakes C, Markmann E, Palanjian M, Cullison K, Tiao J, Kapoor S, Liu CY, Naji A, Teff KL. Restoration of glucose counter regulation by islet transplantation in long-standing type 1 diabetes. Diabetes. 2015;64(5):1713-1718.
[19]. Hering BJ, Clarke WR, Bridges ND, et al. Phase 3 trial of transplantation of human islets in type 1 diabetes complicated by severe hypoglycemia. Diabetes Care. 2016;39(7):1230-1240.