Lifestyle vs Transplantation Therapies Aiding in Pancreatic Beta Cell Protection for Type 1 Diabetes

Micah Stierli[1], Ali Abdalbari and Arya Pore

[1]Shasta College

ABSTRACT

Pancreatic beta cells highly influence the level of insulin within the body. This being due to the beta cell's ability to create and regulate the production of insulin (the hormone that manages blood sugar extent). Unfortunately, the increasing death rate of these cells has complicated insulin independence for people with type 1 and type 2 diabetes. Type 1 diabetes (T1D) continues to be a serious concern considering the globally growing incidence rate and the regard that there is no currently confirmed cure. However, multiple new cellular therapies have been explored and evaluated to aid in beta cell regeneration strategies. This literature review focuses specifically on commonly practiced beta cell regeneration therapies for type 1 diabetes. These therapeutic approaches were divided to fit into one of two categories, these categories being cellular reproduction and cell replacement which will be further expanded on throughout this article. Topics discussed within the work aim to exhibit a brief overview of the type 1 diabetes patient population, beta cell pathophysiology, and cover concepts regarding methods of measuring procedural success. The majority of this article will be centered around commonly practiced clinical strategies involving pancreas/islet cell transplantation and therapeutic lifestyle approaches. All this is concluded with a general comparison of typical beta cell therapies.

Introduction

Diabetes mellitus is a well known chronic disease that is common among individuals around the world. This condition is brought on by a person's body lacking the ability to sufficiently utilize or produce insulin in order to integrate glucose into the bloodstream. (CDC, 2022) The hormone insulin is constructed within pancreatic B-cells in order to serve as a gateway for allowing glucose into the body's cells for energy usage. Diabetes in general is broken up into two different classifications which are type 2 diabetes (T2D) and type 1 diabetes (T1D). (Jeyagaran et al., 2022) T2D is brought on by cells within the body becoming unable to ordinarily react to insulin, thus, resulting in insulin resistance. The pancreas then generates additional insulin in an attempt to invoke a response from these cells. Ultimately, this leads to unfavorable increasing blood sugar levels promoting the advancement of developing prediabetes and T2D. (CDC, 2023) Although, in T1D, insulin is not able to be produced from the pancreas on account of the body's immune system attacking the B-cells responsible for creating insulin.

The difference in treatment methods between T1D and T2D, is that T2D is preventable and manageable when maintaining healthy levels of weight, diet, and exercise. However, T1D is still currently unpreventable and incurable. This raises concern bearing in mind there were roughly 8.4 million people identified worldwide to have type 1 diabetes in the year 2021 along with the existence of type 1 diabetes being predicted to increase significantly with extrapolation into the year 2040. (Gregory et al., 2022) Those with uncontrolled T1D are at risk for developing various complications to their overall health. These can often lead to debilitating disabilities or even death. Such complications are cardiopulmonary issues, nerve damage in extremities, kidney, eye, and foot damage, as well as skin conditions. (*Type 1 diabetes*, 2023) Finding treatments that prevent the necrosis of pancreatic beta cells can improve the lives of many at risk of developing diabetes to where they don't have to experience the damaging symptoms and limitations associated with a T1D diagnosis.

Patient Population

In this study, the control group that was analyzed for this literature review were individuals over 18 with Type 1 Diabetes (T1D). In terms of age, the rate of T1D diagnosis after puberty declines and stabilizes in young adults around 15-29 years of age. (Maahs et al., 2010) Being diagnosed with T1D in adulthood is much less common than being diagnosed in childhood, where approximately 75% of individuals with T1D are diagnosed in their childhood years.(Maahs et al., 2010) It has been found that the global incidence rate of T1D has increased by 2-5% where approximately 1/300 individuals in the USA have T1D by 18 years of age. (Maahs et al., 2010) To add, in a Canadian Heart Health (CHH) survey, the incidence rate of self-reported T1D in individuals 18-74 years of age is approximately 5.1%. (Tao et al., 2015)

It is not known if the sex of individuals has an effect on the rate of T1D in adults and it is assumed, (with the knowledge of T1D now) that males and females are affected equally with T1D. However, it has been reported that in some areas of the world with high incidence rates of T1D, such as those of European origins, males are more likely to be affected with T1D.(Maahs et al., 2010) Similarly, those with areas of low incidence, report that females are more likely to be affected with T1D.(Maahs et al., 2010) To add, other reports indicate that those that are newly diagnosed over pubertal age are more likely to be male. (Maahs et al., 2010)

Race and ethnicity have been shown to have an effect on one's susceptibility to developing diabetes in their lifetime. This can be due to factors such as body type, diet, lifestyle, and genetics. (McQueen et al., 2023) In terms of body type, certain ethnicities carry weight on the body differently as it depends on how much of one's body weight comes from fat and where it is stored on the body. (McQueen et al., 2023) This is what makes obesity a major factor of developing diabetes. It is known that the diet and lifestyle of certain cultures can be deemed more healthy or sustainable when it comes to exercise or the types of food within that environment. The rates of diagnosed diabetes in adults by race and/or ethnic background reported by the American Diabetes Association are as follows:

- 14.5% of American Indians/Alaskan Natives
- 12.1% of non-Hispanic blacks
- 11.8% of Hispanics
- 9.5% of Asian Americans
- 7.4% of non-Hispanic whites

A Type 1 Diabetes (T1D) diabetes diagnosis is no doubt very distressing to any individual as it poses symptoms and limitations in their everyday life. The Mayo Clinic lists potential symptoms of T1D that include (*Type 1 diabetes*, 2023):

- Feeling more thirsty than usual
- Urinating a lot
- Bed-wetting in children who have never wet the bed during the night
- Feeling very hungry
- Losing weight without trying
- Feeling irritable or having other mood changes
- Feeling tired and weak
- Having blurry vision

Pancreatic Beta Cell

As one develops and grows the rate at which pancreatic beta cells die may lead to a diabetes diagnosis. The beta cell mass available in the pancreas determines whether one has normal insulin secretion, type 2 diabetes or type 1 diabetes. A study conducted on β-cell death in diabetes, indicated that type 1 diabetics have an approximately doubled rate of pancreatic cell death than those with normal pancreatic function, which were the control subjects in this study. (Mukherjee et al., 2021) Along with this increased rate of beta cell death, there was a high presence of islet macrophages and T lymphocytes.(Mukherjee et al., 2021) Overall, it was found that a newly diagnosed type 1 diabetic would have a reduction of 70-80% of pancreatic beta cell mass compared to normal individuals and that beta cell loss occurs over an extended period of time. (Mukherjee et al., 2021)

The different ways the insulin-producing pancreatic beta cell death occurs are complex and include different genetic, immunological, and environmental factors. The exact factors and mechanisms in which cell death occurs are still unknown but they can be speculated. These may be due to mechanisms including autoimmune responses, cytotoxic T cells, inflammation and cytokines, apoptosis and endoplasmic reticulum stress, oxidative stress, viral infections, genetic factors, and/or environmental triggers. (Cnop et al., 2005)

It is thought that the primary mechanism in which beta cell death occurs in type 1 diabetes is through an autoimmune response. This is done by the immune system mistakenly attacking the beta cells. This autoimmune response is done by autoreactive T cells and antibodies that attack beta cell antigens such as insulin, GAD65, IA-2. (Cnop et al., 2005) The immune response in Type 1 diabetes can cause the release of proinflammatory cytokines like interleukin-1 beta, tumor necrosis factor-alpha, and interferon-gamma which promote apoptosis, inflammation, and destruction and reduction of beta cell function. (Cnop et al., 2005)

Autoreactive cytotoxic T cells are responsible for identifying and removing unfunctional or irregular beta cells by inducing apoptosis or cell death. (Cnop et al., 2005) This ultimately removes and kills the pancreatic beta cell. This is done through the release of perforins and granzymes. (Cnop et al., 2005)

Viral infections and environmental triggers influence and induce different activities in the immune system that therefore affect beta cell functionality (10). Viral infections can trigger an overactive immune system to attack the beta cells through the mechanism described above. (Cnop et al., 2005) Environmental triggers like diet, lifestyle, and toxin exposure can cause a T1D diagnosis by influencing the immune system and promoting beta cell autoimmunity.

A blood test called the C-peptide blood test is used to measure the amounts of pancreatic beta cells and their functionality. (Hashmi et al., 2018) These can usually concur whether an individual had diabetes or not. C-peptide is an amino acid chain that is released in the blood as a byproduct of insulin production and formation of the pancreas. (Hashmi et al., 2018) The pancreatic beta cells take a proinsulin molecule and split it apart to form one molecule of C-peptide and one molecule of insulin; this is crucial for the transportation of glucose. (Hashmi et al., 2018) Therefore, when the beta cells produce insulin, there is an equal amount of C-peptide molecules in the bloodstream as they are produced at the same time. (Hashmi et al., 2018) This makes the C-peptide a good marker for insulin production and therefore used as a way to evaluate the amount of insulin the pancreas makes.

Regenerative B-Cell Therapies

Cell Reproduction

The reproduction of damaged cells following injury, is a critical aspect of regenerative medicine and holds promise for addressing the challenges posed by Type 1 Diabetes (T1D). In T1D, the autoimmune destruction of pancreatic beta cells leads to insulin deficiency, necessitating the restoration of these cells for effective treatment. (Burrack et al.,

2017) To achieve successful cell reproduction, various factors must be considered. Commonly recognized replenishing factors include dietary interventions, exercise regimes, and pharmacological agents.

Dietary Interventions

The integration of targeted dietary interventions holds significant potential to enhance the efficacy of regenerative B-cell therapies in the context of Type 1 diabetes (T1D). Recent studies suggest that a low-calorie or fasting-mimicking diet could induce a regenerative response in pancreatic β-cells, potentially augmenting the outcomes of regenerative therapies. (Zhong & Jiang, 2019) Additionally, a diet rich in specific nutrients such as omega-3 fatty acids and vitamin D has been implicated in promoting immune tolerance and dampening autoimmune responses. Furthermore, the manipulation of carbohydrate sources and fiber intake could influence gut microbiota composition, fostering an environment conducive to β-cell regeneration and immunomodulation. These nuanced dietary approaches, when synergistically combined with regenerative therapies, hold promise in addressing the multifaceted challenges of T1D treatment, potentially leading to improved β-cell regeneration, sustained immunological balance, and enhanced long-term therapeutic effects.

Exercise Regimes

Incorporating specific exercises as interventions to regenerative B-cell therapies for Type 1 diabetes presents a nuanced approach for optimizing treatment outcomes. (Paula et al., 2015) Aerobic exercise, characterized by its capacity to enhance insulin sensitivity and cardiovascular fitness, may facilitate an environment conducive to β-cell regeneration through improved glucose metabolism and anti-inflammatory effects. Resistance training, on the other hand, offers the potential to augment muscle mass, thus elevating metabolic rate and promoting glucose control, which could support long-term β-cell function. Additionally, high-intensity interval training's unique ability to stimulate mitochondrial biogenesis and stress adaptation might contribute to the preservation and functionality of β-cells. Mind-body practices, including yoga, provide an invaluable avenue for reducing stress and fostering psychological well-being, factors that are pivotal for promoting an immune-permissive milieu necessary for the success of regenerative therapies. Tailoring exercise prescriptions according to individual characteristics ensures the precise amalgamation of these modalities, collectively working in synergy with regenerative approaches, and paving the way for a comprehensive paradigm shift in Type 1 diabetes management.

The diverse array of exercise modalities underscores the importance of patient-centered approaches in guiding exercise interventions. Personalized exercise regimens, designed with consideration of factors such as age, fitness level, and existing medical conditions, guarantee both safety and efficacy. Continuous monitoring of glucose levels throughout exercise becomes crucial in avoiding fluctuations that might impact overall glycemic control. Collaboration among healthcare professionals, exercise specialists, and individuals with Type 1 diabetes plays an instrumental role in tailoring exercise protocols that harness the distinct advantages of each modality, ultimately contributing to the optimization of regenerative B-cell therapies for better patient outcomes and an enhanced quality of life.

Pharmacological Agents

Glucagon-like peptide-1 (GLP-1). GLP-1, currently under investigation, has shown potential in stimulating beta cell proliferation and insulin secretion. (Xinrui et al., 2023) Clinical procedures involving regenerative approaches often involve the administration of GLP-1 analogs in combination with other therapeutic strategies. These strategies encompass patient-specific dietary modifications to provide the necessary nutrients for cell regeneration and exercise routines that enhance metabolic health and facilitate tissue repair.

Effectively reproducing pancreatic beta cells can be done with two strategies which have their own advantages and disadvantages. One method involves implanting pancreatic progenitor (PP) cells, which later differentiate into sBCs via mainly unidentified cues derived from in vivo. The therapeutic functional mass is reached after months of this in vivo maturation phase, and grafts show significant cellular heterogeneity with varying contributions from different pancreatic and PP cells . But these results were enough to spur a first-in-human clinical investigation. The in vitro creation of sBCs is an alternate strategy that offers the benefits of more rapid graft function, a smaller overall transplant volume, and a specified cell product at the moment of transplantation. (Brusko et al., 2021)

Cell Replacement

There are several forms of beta cell replacement strategies. (Chen et al., 2020) The commonly accepted strategies used in current clinical practice are transplantation procedures such as islet transplantations and pancreas transplantations. Transplantations are conducted within a carefully chosen grouping of patients with T1D that are living with chronic extreme hypoglycemia. (Bellin & Dunn, 2020) This is because essential anti-rejection drugs taken following the transplant procedure could potentially have more severe effects than T1D. In addition, there are potential risks of pancreas rejection. (Mantovani et al., 2023) For this reason, the advantages and risks of transplantation should be thought through thoroughly before coming to a definite decision. Factors that determine the type of transplantation procedure can vary from, islet and pancreas availability, to treatment objectives and patient attributes. The most frequently discussed transplantation models are further broken down within this section.

Pancreas Transplant

Whole Pancreas transplantation is a major clinical procedure that involves transferring a healthy insulin producing pancreas organ into a person whose own pancreas does not have the ability to supply the necessary amount of insulin. (*Pancreas transplant*, 2022) The new pancreas organ is acquired one of two ways from either a deceased benefactor or a segment of a whole pancreas from a living donor. This operation possesses a strong possible outcome for insulin independence and discontinuation of hypoglycemia. Another benefit of a pancreas transplant procedure is that it may assist in regulating injuries done to other organs such as the kidneys. Pancreas transplantation has ordinarily been conducted alongside kidney transplantation due to T1D often coinciding with extreme kidney disease. Consideration for transplantation also extends to alternatively fatal complications resulting from unmanageable glucose levels. When a patient exhibits critically unstable T1D, they might even be evaluated for a lone pancreas transplantation.

Islet Transplant

Islets can be defined as well vascularized configurations containing a compact system of capillaries as well as blood vessels. These are used for aiding in the movement of molecules like growth factors, hormones, and oxygen. In between cellular islets and capillaries are nerve fibers which play a part in managing insulin generation and secretion. (Koma et al., 2008) Pancreatic islets used in transplantation are acquired from pig or cadaver pancreas organs. The islets are then extracted from the donors to go through specialized isolation procedures in order to obtain top-grade islets. (Bellin & Dunn, 2020) Currently, there have been prospects involving utilizing stem cells in differentiating insulin-generating cells as a beginning initiative towards transplanting islets. These strategies of cell differentiation and islet isolation procedures allow for the islets to be transplanted into bodily areas such as the kidney, spleen, liver, pancreas, etc. Transplantation location is incredibly important for overall islet graft performance and survival rate. In smaller animal studies the size of the transplant generally did not exhibit any complications due to the amount of islets not being a limiting component to the rate of diffusion or area. (Jeyagaran et al., 2022) Although, in humans the amount of islets can immensely affect the transplant location, this being because a larger number of islets are needed.

In order to efficiently monitor the procedural process the transplantation site must allow for low amounts of natural and adjustable immune responses, this is important for facilitating the new formation of blood vessels. The location should also allow for the transplant to be minorly invasive. (Bellin & Dunn, 2020)

Transplant Comparison

Determining the functionality of varying treatment therapies for beta cell rehabilitation has been an ongoing effort for years and continues to change with newly developing advancements. Patients with T1D are able to routinely check their own blood glucose levels daily by utilizing continuous glucose monitoring technology. (Cleveland Clinic., 2017) This type of glucose management system presents a potential way to gather data for analyzing treatment benefits associated with beta cell therapies. (Ajjan et al., 2019)

Although pancreas transplants are observed to have a high rate of success resulting in elevated levels of graft continuity and align additionally with the therapeutic goal of achieving insulin independence, these operations are restricted due to the shortage of qualified donors. (Chen et al., 2020) Pancreas transplants also present possible risk factors associated with any invasive surgery.

Transplantation using pancreatic islets obtained from donors presents considerable potential for remedying T1D. (Bellin & Dunn, 2020) This sort of procedure is greatly advantageous for treating hypoglycemia, however, multiple pancreatic donors might be needed to gain insulin independence. A couple of other advantages to this procedure include it being a minor operation with possibility for encapsulation. The disadvantages to this transplantation, however, were reported to be a delayed commencement in functional activity. (Bellin & Dunn, 2020) Recently, scientists have been studying possible islet transplantation with non-human primates. For example, pig islets (porcine islets) offer a possible continuous supply of islets. These porcine islets were proven to be able to treat diabetes found in non-human primates while applying proper immunosuppressive conditions, yet still more data is required to allow for human studies. (Bellin & Dunn, 2020)

Measurement of procedural success

Commonly recognized approaches to β cell replacement therapy include islet cell and pancreas transplantation. However, the parameters for evaluating the results in these standardized replacement therapies were not clearly confirmed until January 2017 in Igls, Austria. To establish a baseline for measuring the efficiency of beta cell therapy options, the International Pancreas & Islet Transplant Association (IPITA) collectively worked alongside the European Pancreas and Islet Transplant Association (EPITA) to construct a shared statement consensus defining the outcomes of beta cell transplantation therapies. (Piemonti et al., 2018) The method of assessment proposed to determine the treatment success rate was a four tiered classification system. In this classification structure, optimal β-cell graft function is interpreted to be close to normal glycemic control determined by nondiabetic HbA1c levels of 6.5% or less (48 mmol/mol) with no presence of extreme hypoglycemia, as well as no need for exogenous insulin. In what is considered good beta cell graft function HbA1c levels are of 7.0% or less (53 mmol/mol) with no presence of extreme hypoglycemia, along with a decline of over 50% from usual insulin requirements. Marginal beta cell graft function however, is the failure to obtain HbA1c levels of 7.0% or less (53 mmol/mol) accompanied with the existence of any extreme hypoglycemia, or a decline in insulin requirements smaller than 50%. Overall beta cell graft failure is defined by the lack of any proof of the procedure having a clinical impact. (Piemonti et al., 2018) With the clearly outlined and quantifiable variables, comparing procedural results following contrasting beta cell replacement therapies is now possible.

Continuous glucose monitoring data can assist in deciding individual treatment options and evaluating the results/benefits of treatment. However, this collected data has not been utilized in a way to determine a treatment's failure or success rate as of yet. (Ajjan et al., 2019)

Conclusion

Based on information our group gathered from accessible data, pancreas transplantation is currently the most effective procedure. This is because pancreas transplantation holds great possibility for achieving insulin independence. Despite the procedure being considerably invasive, it possesses a long-term solution for T1D patients that meet certain operational criteria. Pancreas transplantation in general exhibits a >95% patient survival rate after 1 year as well as a >88% success rate 5 years following the operation. (Gruessner & Gruessner, 2013) Although islet transplantation is also a promising therapy, patients still present under optimal results and the procedure requires further innovations to become reliable long-term. (Vardanyan et al., 2010)

The results of exercise, dietary, and pharmacological beta cell therapies were inconclusive in terms of efficiency. This is because countless lifestyle variables and other factors such as race, gender, and hereditary susceptibility can contribute to an individual's glucose levels. Measuring how activity or nourishment affects one T1D patient may be completely different from the outcomes of another. (Cleveland Clinic., 2017) Overall, changes in livelihood do not present a conclusive solution to T1D.

Methods

Publication searches for basic foundational information on the topic were managed first through Google Scholar using keywords such as type 1 diabetes, beta cell, pancreas, islet cell, and transplant. For data sources to gather current population statistics and diagnosis rates, we compared information from the American Diabetes Association as well as the Centers for Disease Control and Prevention. In-depth data relating to T1D incidence rates was found by conducting a search through the National Library of Medicine. This allowed us to include information from the most recent global incidence study, published through the NIH, in the form of a systematic review. We adhered to this systematic review which analyzed all globally reported adult T1D population studies within the Embase and Medline databases. These studies examined in the referenced systematic review were published between the years 1990 and beyond. (Harding et al., 2022)

Limitations

The data regarding T1D cases in adult onset was limited due to T1D being historically identified as an adolescent disease as well as T1D being less common than T2D. Because of this, there is still significant uncertainty in the amount of adult diagnosis cases. This review does not incorporate a thorough analysis of therapies such as gene therapy, stem cell therapy, and immunotherapies.

Acknowledgements

We would like to acknowledge and thank the Medicine for Youth nonprofit organization for conducting the summer research program which gave us this opportunity to conduct this literature review.

References

Ajjan, R., Slattery, D., & Wright, E. (2019). Continuous Glucose Monitoring: A Brief Review for Primary Care Practitioners. *Advances in therapy*, *36*(3), 579–596. https://doi.org/10.1007/s12325-019-0870-x

Bellin, M. D., & Dunn, T. B. (2020). Transplant Strategies for Type 1 diabetes: Whole pancreas, islet and porcine beta cell therapies. *Diabetologia*, *63*(10), 2049–2056. https://doi.org/10.1007/s00125-020-05184-7

Brusko, T. M., Russ, H. A., & Stabler, C. L. (2021). Strategies for durable β cell replacement in type 1 diabetes. *Science (New York, N.Y.)*, *373*(6554), 516–522. https://doi.org/10.1126/science.abh1657

Burrack, A. L., Martinov, T., & Fife, B. T. (2017). T Cell-Mediated Beta Cell Destruction: Autoimmunity and Alloimmunity in the Context of Type 1 Diabetes. *Frontiers in Endocrinology*, *8*(343). https://doi.org/10.3389/fendo.2017.00343

CDC. (2023, April 18). *Type 2 Diabetes*. Centers for Disease Control and Prevention. https://www.cdc.gov/diabetes/basics/type2.html

Centers for Disease Control and Prevention. (2022, March 11). What is type 1 diabetes?. Centers for Disease Control and Prevention. https://www.cdc.gov/diabetes/basics/what-is-type-1-diabetes.html

Chen, S., Du, K., & Zou, C. (2020). Current progress in stem cell therapy for type 1 diabetes mellitus. *Stem cell research & therapy*, *11*(1), 275. https://doi.org/10.1186/s13287-020-01793-6

Cleveland Clinic. (2017). *Continuous Glucose Monitoring | Cleveland Clinic*. Cleveland Clinic. https://my.clevelandclinic.org/health/drugs/11444-glucose-continuous-glucose-monitoring

Cnop, M., Welsh, N., Jonas, J.-C., Jo¨rns, A., Lenzen, S., & Eizirik, D. L. (2005). Mechanisms of pancreatic β-cell death in type 1 and type 2 diabetes. Diabetes, 54(suppl_2), S97–S107. https://doi.org/10.2337/diabetes.54.suppl_2.s97

Gregory, G. A., Robinson, T. I. G., Linklater, S. E., Wang, F., Colagiuri, S., Beaufort, C. de, Donaghue, K. C., Magliano, D. J., Maniam, J., Orchard, T. J., Rai, P., & Ogle, G. D. (2022). Global incidence, prevalence, and mortality of type 1 diabetes in 2021 with projection to 2040: a modelling study. *The Lancet Diabetes & Endocrinology*, *10*(10), 741–760. https://doi.org/10.1016/S2213-8587(22)00218-2

Gruessner, R. W. G., & Gruessner, A. C. (2013). The current state of pancreas transplantation. *Nature Reviews. Endocrinology*, *9*(9), 555–562. https://doi.org/10.1038/nrendo.2013.138

Harding, J. L., Wander, P. L., Zhang, X., Li, X., Karuranga, S., Chen, H., Sun, H., Xie, Y., Oram, R. A., Magliano, D. J., Zhou, Z., Jenkins, A. J., & Ma, R. C. W. (2022). The Incidence of Adult-Onset Type 1 Diabetes: A Systematic Review From 32 Countries and Regions. *Diabetes care*, *45*(4), 994–1006. https://doi.org/10.2337/dc21-175

Hashmi, A. (2018, November 17). A simple way to calculate beta cell functional decline in diabetes. Diabetes In Control. A free weekly diabetes newsletter for Medical Professionals. https://www.diabetesincontrol.com/a-simple-way-to-calculate-beta-cell-functional-decline-in-people-with-diabetes/#:~:text=The%20C%2Dpeptide%20test%20is,the%20autoimmune%20type%201%20diabetes

Jeyagaran, A., Lu, C. E., Zbinden, A., Birkenfeld, A. L., Brucker, S. Y., & Layland, S. L. (2022). Type 1 diabetes and engineering enhanced islet transplantation. *Advanced drug delivery reviews*, *189*, 114481. https://doi.org/10.1016/j.addr.2022.114481

Jeyagaran, A., Lu, C., Zbinden, A., Birkenfeld, A. L., Brucker, S. Y., & Layland, S. L. (2022). Type 1 diabetes and engineering enhanced islet transplantation. *Advanced Drug Delivery Reviews*, *189*, 114481. https://doi.org/10.1016/j.addr.2022.114481

Koma, Y., Furuno, T., Hagiyama, M., Hamaguchi, K., Nakanishi, M., Masuda, M., Hirota, S., Yokozaki, H., & Ito, A. (2008). Cell Adhesion Molecule 1 Is a Novel Pancreatic–Islet Cell Adhesion Molecule That Mediates Nerve–Islet Cell Interactions. *Gastroenterology*, *134*(5), 1544–1554. https://doi.org/10.1053/j.gastro.2008.01.081

Maahs, D. M., West, N. A., Lawrence, J. M., & Mayer-Davis, E. J. (2010). Epidemiology of type 1 diabetes. Endocrinology and Metabolism Clinics of North America, 39(3), 481–497. https://doi.org/10.1016/j.ecl.2010.05.011

Mantovani, M. da C., Gabanyi, I., Pantanali, C. A., Santos, V. R., Corrêa-Giannella, M. L. C., & Sogayar, M. C. (2023). Islet transplantation: overcoming the organ shortage. *Diabetology & Metabolic Syndrome*, *15*(1). https://doi.org/10.1186/s13098-023-01089-8

Mayo Foundation for Medical Education and Research. (2023, May 3). Type 1 diabetes. Mayo Clinic. https://www.mayoclinic.org/diseases-conditions/type-1-diabetes/symptoms-causes/syc-20353011

McQueen, J. (2023, July 7). Type 2 diabetes: How race plays a part. WebMD. https://www.webmd.com/diabetes/type-two-diabetes-race

Mukherjee, N., Lin, L., Contreras, C. J., & Templin, A. T. (2021, November 22). B-cell death in diabetes: Past discoveries, present understanding, and potential future advances. Metabolites. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8620854/#:~:text=In%20their%202003%20study%20of,%2Ddiabetic%20controls%20%5B37%5D

Pancreas transplant - Mayo Clinic. (2022). Mayoclinic.org. https://www.mayoclinic.org/tests-procedures/pancreas-transplant/about/pac-20384783

Paula, F. M. M., Leite, N. C., Vanzela, E. C., Kurauti, M. A., Freitas-Dias, R., Carneiro, E. M., Boschero, A. C., & Zoppi, C. C. (2015). Exercise increases pancreatic β-cell viability in a model of type 1 diabetes through IL-6 signaling. *The FASEB Journal*, *29*(5), 1805–1816. https://doi.org/10.1096/fj.14-264820

Piemonti, L., de Koning, E. J. P., Berney, T., Odorico, J. S., Markmann, J. F., Stock, P. G., & Rickels, M. R. (2018). Defining outcomes for beta cell replacement therapy: a work in progress. *Diabetologia*, *61*(6), 1273–1276. https://doi.org/10.1007/s00125-018-4588-0

Tao, Z., Shi, A., & Zhao, J. (2015). Epidemiological perspectives of diabetes. Cell Biochemistry and Biophysics, 73(1), 181–185. https://doi.org/10.1007/s12013-015-0598-4

Vardanyan, M., Parkin, E., Gruessner, C., & Rodriguez Rilo, H. L. (2010). Pancreas vs. islet transplantation: a call on the future. *Current Opinion in Organ Transplantation*, *15*(1), 124–130. https://doi.org/10.1097/mot.0b013e32833553f8

Xinrui , T., Xiongfeng , P. X., Xiaochuan, W., Songjia, Z., Yuyao, C., Donghai, L., & Xingxing, Z. (2023). Glucagon-like peptide-1 receptor agonists as add-on therapy to insulin for type 1 diabetes mellitus [Review of *Glucagon-like peptide-1 receptor agonists as add-on therapy to insulin for type 1 diabetes mellitus*]. *Frontiers in Pharmacology*, *14*(1663-9812). Frontiers.org. https://doi.org/10.3389/fphar.2023.975880

Zhong, F., & Jiang, Y. (2019). Endogenous Pancreatic β Cell Regeneration: A Potential Strategy for the Recovery of β Cell Deficiency in Diabetes. *Frontiers in Endocrinology*, *10*, 101. https://doi.org/10.3389/fendo.2019.00101