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PANCREATIC ISLET TRANSPLANTATION IN THE TREATMENT OF  
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## PANCREATIC ISLET TRANSPLANTATION IN THE TREATMENT OF TYPE I DIABETES

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## ABSTRACT

Type I diabetes is a chronic autoimmune disease characterized by a complete lack of insulin secretion due to damage to pancreatic beta cells. Despite the development of new methods of glycemic monitoring and intensive insulin therapy, traditional treatment does not lead to a complete cure, and therefore does not completely rule out the occurrence of complications such as hyper- or hypoglycemia. An unconventional therapeutic method is pancreatic islet transplantation, which makes it possible to restore the physiological secretion of insulin by the pancreas. This article presents the history of the development of islet transplantation and reviews the latest discoveries regarding the technique of islet isolation and transplantation, current transplant sites, and the difficulties associated with donor shortages and immunosuppression. Also discussed are ways to improve the survival and function of transplanted islets, which include the use of mesenchymal stem cells, encapsulation techniques and Treg lymphocytes. Special attention is given to research on insulin-producing cells derived from human pluripotent stem cells, and the results of clinical trials demonstrating the benefits of this method in reducing the risk of hypoglycemia and increasing metabolic control are summarized. Failures associated with achieving incomplete independence from exogenous insulin are also discussed. Pancreatic islet transplantation remains a promising, albeit still experimental, treatment for type I diabetes, requiring further research and refinement.

**Materials and Methods:** This article presents a comprehensive review of literature derived from the PubMed database, encompassing studies published between 2018 and 2025.

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## KEYWORDS

Diabetes Mellitus, Type 1, Islets of Langerhans Transplantation, Pancreatectomy Methods, Pancreatic Diseases Surgery

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## 1. Introduction

Diabetes mellitus is one of the most common diseases in the world. According to data published by the WHO, 440 million people worldwide will suffer from the disease in 2022, and the number of deaths due to it annually is 1.6 million. In Poland, more than 3 million people suffer from diabetes, of which about 750,000 are unaware of their disease [5]. The disorder is associated with abnormal glucose metabolism, resulting in chronic elevated blood glucose levels. There are several types of diabetes, but the most common are type I diabetes and type II diabetes.

Type I diabetes is a disease classified as an autoimmune disorder.[1] In Poland, about 200,000 people suffer from this type of diabetes. These patients account for about 10% of all cases. The peak incidence is between the ages of 10 and 14.[3] The disease is associated with a complete lack of insulin secretion by the pancreas, the cause of which is the malfunction of pancreatic beta cells, which are destroyed by autoimmune processes. These processes are influenced by genetic predisposition and environmental factors. Genetic predisposition is associated with the HLA gene complex located on the shorter arm of chromosome 6p21 (IDDM1). The major role of allelic variation in the HLA-DRB1, HLA-DQA1 and HLA-DQB1 class II loci has been established [1], as well as a second component of IDDM1 on the HLA class I region[2]. In addition to this, analyses of the human genome have shown that Treg lymphocytes also influence the occurrence of the disease, however, the mechanism of loss of control of these lymphocytes has not yet been understood. [1]. Among the environmental factors predisposing to type I diabetes are childhood infections, pre-diabetic status during pregnancy, a positive family history of the disease in the family and vitamin D3 deficiency.[3] The disease develops rapidly, and its first symptoms include increased thirst, polyuria, weight loss or irritability and general weakness.

## 2. Traditional treatment methods

Conventional treatment of type I diabetes is based on blood glucose control and continuous insulin intake by subcutaneous injection, as well as nutrition training. Psychosocial care is also often useful, especially at the beginning of diagnosis. Insulin requirements in patients are individually variable and should be tailored to the patient. Among the variables affecting this are the physiological secretion of insulin or the insulin sensitivity of the individual patient. Functional insulin therapy, otherwise known as intensive therapy, is based on the administration of at least three subcutaneous injections of insulin per day. It usually involves the administration of two types of insulin, i.e. long-acting insulin, known as basal insulin, which is designed to supplement basal insulin requirements, and rapid-acting insulin, which covers insulin requirements that occur as a result of eating. Due to the way insulin is obtained, there are types of insulin available: human insulin, animal insulin and insulin analogs. [6]. Because of the reduced risk of hypoglycemia, it is recommended that patients with type I diabetes be treated with analogs. [5] For self-administration of insulin, patients use pens or a personal insulin pump. Unfortunately, good diabetes control does not preclude the occurrence of acute diabetes complications, which include hypo- and hyperglycemia. Moreover, conventional diabetes therapy does not cure the disease and must be used for the rest of life. More and more researchers are paying attention to the alternative treatment for diabetes which is pancreatic islet transplantation. Observations of the results of reports on this subject show that it provides significant benefits in the treatment of diabetes[7].

## 3. Pancreatic islet transplantation as a new treatment for type I diabetes

Pancreatic islet transplantation (IT) is a procedure in which pancreatic islets are isolated and purified from a donor pancreas and infused subcutaneously into the patient's liver via a portal vein. This pancreas does not have to be xenogeneic. It forms an endogenous, glucose-dependent insulin secretion system in the donor's body, which restores physiological insulin secretion patterns. In this way, the patient is able to achieve accurate glucose control in real time [7,8]. It has been shown that this procedure can be more effective in delaying diabetes-related complications and leads to better metabolic control. [8].

## 4. Transplant history

Pancreatic islet transplantation, as a treatment for diabetes, emerged in the 19th century. Its precursor was the pancreatic discovery by Oskar Minkowski. He performed a total pancreatectomy in dogs and noted the development of glucosuria immediately after the operation. Subsequently, Emmanuel Hedon, continuing his research, demonstrated that the pancreas functions after transplantation if an adequate vascular supply is transplanted along with it. The first attempt at pancreas transplantation in humans was made in 1893 by Watson-Williams transplanting pancreas fragments from a sheep to a 13-year-old patient; however, the experiment failed and the patient died after a few days. The early 1900s saw improvements in the understanding of pancreatic islets and their role in insulin secretion, but it wasn't until 1960 that a breakthrough was made, when Horaguchi and Merrell introduced the technique of perfusing the pancreas with collagenase to separate islets from the collagen matrix. In 1980, meanwhile, the first transplant of human pancreatic islet cells was performed in 10 patients after pancreatectomy for chronic pancreatitis. Nine patients survived the procedure and subsequently maintained normoglycemia for a period of 38 months. Unfortunately, these patients required high doses of steroids for immunosuppression, and this was associated with many side effects. In 2000, another breakthrough occurred when Dr. James Shapiro and his team developed the Edmonton Protocol for pancreatic islet cell transplantation and introduced an immunosuppression regimen without glucocorticosteroids. [9]

## 5. Sources of pancreatic islets

Pancreatic islet transplantation usually uses a pancreas taken from a deceased donor.

The procedure involves the isolation of pancreatic islet cells capable of producing insulin from a donor i.e. autologous source or from autologous sources, which include complete pancreatic resection resulting from pancreatitis or due to trauma. Islets are extracted from the pancreas using contamination chemical methods, including digestion with collagenase and natural protease, and mechanical methods. The next step is to purify the islets using various centrifugations, the purpose of which is to separate the islets from the alveolar and ductal tissue of the pancreas. The islets thus prepared are transplanted into the liver using percutaneous transhepatic islet transplantation at portal vein sites. Currently, the liver is the preferred site for transplantation due to the low invasiveness of the procedure, as well as the low rate of thrombosis and bleeding and easy accessibility. [8]

## 6. New methods of acquiring islets

Unfortunately, a huge challenge and a major problem in worldwide pancreatic islet transplants is the shortage of donors. [10] As a result, researchers have begun to look for other solutions to obtain these structures. Intensive research is underway to create insulin-producing cells (IPCs) or islet organoids in vitro using human pluripotent stem cells (hPSCs). The sources for obtaining IPC cells or organoids are mainly human embryonic stem cells and human induced pluripotent stem cells, adult stem cells and differentiated cells from mature tissues that can be transdifferentiated into IPCs. The goal of all efforts is to create IPC cells under conditions that mimic the natural development of the pancreas. The resulting cells must have individual biological markers of standard pancreatic  $\beta$ -cells that identify the state of terminal differentiation, such as MAFA (basic leucine lock transcription factor expressed in mature  $\beta$ -cells and absent in pancreatic progenitors and other cell types), NEUROD1 (downstream factor NGN3 expressed in most pancreatic endocrine cells, including  $\beta$ -cells) and PDX1/NKX 6.1 (limited coexpression in  $\beta$  cells), as well as key functional features of adult  $\beta$  cells, including glucose-stimulated insulin secretion (GSIS) and C-peptide secretion [10-12]. Researchers confirm that human embryonic stem cells and human induced pluripotent stem cells have a predisposition to differentiate into insulin-producing cells, but due to the poor differentiation efficiency of the protocols and the polyhormonal characteristics of these beta-like cells, scientists remain cautious about deriving pancreatic islets from stem cells. [7]

## 7. Challenges of immunosuppression

Another challenging issue in pancreatic islet transplantation is immune rejection of the recipient organ. It is likely to be the progenitor of the progressive decline in islet function over the years after transplantation and the inability of some patients to completely wean off exogenous insulin. Immunosuppression includes such reactions as immediate blood mediated inflammatory response (IBMIR), recurrent autoimmune reactions, allogeneic rejection and many others. Therefore, the highest quality islets from multiple donors or multiple sources are used during the procedure, with the goal of counteracting significant cell loss after transplantation. To minimize the risk of rejection, not only immunosuppressive drugs are used, but there is also ongoing research into the combined transplantation of mesenchymal stem cells (MSC)/regulatory T cells and islet cells, as well as the use of islet encapsulation techniques. [7] MSC stem cells are cells easily obtained from, for example, human or rodent peripheral blood or umbilical cord blood or placental tissue. They are supposed to improve insulin resistance in peripheral tissues through immunomodulation and anti-inflammatory effects, as well as help regenerate and protect pancreatic  $\beta$  cells. Studies show that transplantation of mesenchymal stem cells together with pancreatic islets protected them from apoptosis resulting from hypoxia and inflammatory cytokines, leading to increased islet graft survival in vivo and enhanced early regeneration. Regulatory T lymphocytes, on the other hand, play a key role in maintaining immune homeostasis, sustaining self-tolerance and limiting over-activation of the immune system. At present, treatment with Treg lymphocytes in pancreatic islet transplantation is recommended in two situations: to increase islet survival in the initial phase of transplantation and to trigger peripheral tolerance to offset immunosuppression. Another method to prevent this problem is lagging with biomaterials that create a protective barrier for the islets. Its goal is to allow oxygen and nutrients to penetrate islet cells while allowing insulin to diffuse into the bloodstream. This method can be divided into: micro-encapsulation and macro-encapsulation, depending on the processes involved. Micro-encapsulation technology facilitates the exchange of nutrients due to the thin layer of biomaterials. According to studies, particularly promising in this method is the use of alginate, which not only reduces the risk of graft rejection, but also increases the survival rate of encapsulated islet cells. The macroencapsulation technique, on the other hand, eliminates direct contact between host cells and donor cells and their agitation. The advantages of this method over microencapsulation are the ability to negate post-transplant safety issues and the ability to control graft efficacy. The disadvantage of this method, however, is the limited exchange of oxygen and other nutrients prior to the formation of blood vessels around the device. [7]

## 8. Islet transplant sites

As of today, the preferred site for islet transplantation is the portal vein of the liver. However, researchers are increasingly questioning this choice as the best site for transplantation due to possible complications such as post-operative bleeding or blood-induced acute reaction. [7,8]. Therefore, work is underway to find an alternative, better site. The site must have three basic characteristics. These are: the presence of innervation and vascularization, accessibility to surgery and the absence of serious surgical complications, and immunomodulatory factors affecting the inflammatory response and elimination of the graft. [8] A potentially

suitable site is the cellular network, which is a highly vascularized tissue that secretes growth factors such as VEGF, SDF-1 or CXCR4, leading to increased vascularization and islet survival. Moreover, it allows monitoring of the graft to prevent overlooking possible adverse effects and has immunomodulatory capabilities.[7] It also has the advantage of accommodating a large volume of islets and biomaterials. [8] Another potential site for transplantation is the subcutaneous space. It is an area where biomaterials or macroscopically surrounded islets can be easily accessed. According to the study, thanks to the use of ESC/iPSC-derived islet-like cells and the encirclement method, this space can be easily observed and removed, which is a great advantage. However, the disadvantage of the subcutaneous cavity is the lack of blood vessels, making it impossible for the skin to obtain oxygen and nutrients at the early stage of transplantation. What's more, transplantation at this site is hindered by the immune response. Therefore, it is necessary to create biomaterials that enable angiogenesis and immune modulation before using this site.[7,13] Another place where researchers are considering the possibility of pancreatic islet transplantation is in the anterior chamber of the ACE eye. It has been used in many types of transplants for 150 years. With its rich vascular network and associated good access to oxygen and nutrients, it enables rapid tissue revascularization. In addition, the procedure at this site its relatively simple to perform and image islets after the procedure. [14] In addition to the aforementioned sites, research is underway into transplanting pancreatic islets into skeletal muscle, intrapleural and other sites. [7]

### 9. Eligibility criteria for transplantation

Pancreatic islet transplantation as a treatment for diabetes is funded by the government in Europe, Canada, China and some parts of Asia. However, through the problem of a shortage of donors, relative to the number of patients with type I diabetes, special criteria have been used to qualify patients for transplantation. These include unawareness of hypoglycemia, glycemic instability, severe episodes of hypoglycemia and/or ketoacidosis despite intensive medical treatment. [15] This type of diabetes is called, "brittle".The next criterion introduced by many centers is the complete loss of patients' c-peptide production [15], age between 18 and 65, and diagnosis made more than 5 years ago. Moreover, researchers have shown that earlier kidney transplantation can increase the effectiveness of the transplant. It is possible that this is due to the use of immunosuppressive treatment after kidney transplantation, which reduces the risk of rejection of islets as well. In contrast, criteria for excluding patients from transplantation include heart disease, uncontrolled hypertension, macroalbuminuria, glomerular filtration rate < 80ml/min/1.73m<sup>2</sup> and potential contraindications to immunotherapy. Currently, there are no studies on the pediatric population. [16,17] In addition, a multicenter study in the Immune Tolerance Network counted the following as exclusion criteria for transplantation: HbA1c greater than 12%, BMI greater than 26 kg/m<sup>2</sup>, insulin requirement >0.7 UI/ kg/day. The Clinical Islet Transplantation consortium study considered as exclusion criteria: BMI>30 kg/m<sup>2</sup>, HbA1c> 10%, and insulin requirement >1.0 UI/kg/day.[18]

### 10. Transplantation procedure

In allogeneic transplantation, ABO system compatibility is assessed, as well as human leukocyte antigen. [16] In the first stage of pancreas procurement, the pancreas is taken from the donor and then preserved for 24 hours in a University of Wisconsin solution. Then, the pancreas goes to an islet isolation center. The process involves cleaning the pancreas of surrounding tissue, and dissecting it to expose the islets of Langerhans. The next step is to cannulate the pancreas and perfuse it with collagenase enzyme solution for 10 minutes to expand it-this helps separate the islets from the separating lining. The pancreas prepared in this way is cut and placed in a special Ricordi chamber. This device was designed to improve the process of islet isolation. Finally, the islets are processed using the COBE 2991 cell processor, which separates the cells from residual exocrine tissue, after which the purified islets are prepared for transplantation. [16] During transplantation, the islets are localized in a special bag, after which they are poured into the portal vein, giving them the opportunity to implant. Using a percutaneous, transhepatic approach, the portal vein is catheterized. Such a method, associated with transplantation of pancreatic islets into the liver, can be associated with a number of complications. Among the most common side effects are: periodic increases in liver test results. A slightly more serious complication, occurring with the highest frequency, is peritoneal or transhepatic hematoma caused by bleeding from the transhepatic duct. Another complication that can occur after transplantation is portal vein thrombosis. It is the greatest concern of medical professionals, however, this complication is relatively rare. A variation on the percutaneous approach is access to the portal vein via laparotomy with catheterization of the mesenteric venous supply. This approach is recommended for patients with a high risk of complications, such as excessive bleeding or thrombophilic disorders.[19]

## 11. Post-transplant results

After transplantation, islets require an extended recovery time. During this time, the patient may still require administration of exogenous insulin. It is likely that transplanted islets will require several months or even years to unite with the recipient's body and establish a vascular supply. This period is particularly prone to the occurrence of attacks from the recipient's immune system, which can reduce the function and survival of the islets. Therefore, during this time, patients must take a combination of immunosuppressive drugs with anti-rejection, maintenance and induction effects. It is important to note that many drugs with these effects also have diabetogenic effects, meaning that they may increase pre-existing metabolic abnormalities in recipients. [16] Braulio Marfil-Garza et al. reported on the results of a long-term study following pancreatic islet transplantation in patients with type I diabetes. The study included 255 transplant patients who were followed for 20 years at the University of Alberta Hospital in Edmonton, Canada. According to this report, post-transplant survival decreases as the years go by, starting at 94% in the first year and then stabilizing at 50% at about 15 years post-transplant. The average graft survival time was 5.9 years. A hemoglobin A1c of less than 7% in the first year after transplantation was achieved in 73.7% of patients, and 20 years after transplantation such results were achieved by 55.5% of those treated. Moreover, a significant reduction in the risk and severity of hypoglycemia was observed throughout the study. Unfortunately, insulin independence one year after transplantation was achieved in 61% of patients, and just four years later it had dropped to 32%. [20]

According to the report, islet transplantation avoids episodes of severe hypoglycemia and significantly reduces insulin requirements. However, these results show that the procedure fails from the perspective of improving glycemic control and graft survival. The goal of transplantation to make patients completely independent of exogenous insulin has also not been achieved and requires further research.[20]

### Conclusions:

Type I diabetes is a serious disease requiring lifelong glycemic control and insulin treatment. Pancreatic islet transplantation is a modern and increasingly well-developed treatment option that allows complete or partial withdrawal of exogenous insulin and reduces the risk of hypoglycemia. Although study results are promising, the long-term efficacy of transplantation remains limited and does not lead to complete insulin independence, due to the gradual loss of islet function over time. The main challenges associated with this treatment method include donor shortage, immunosuppression risks, lack of an ideal transplant site and risk of rejection. This method is not available to everyone and requires strict patient qualification and supervision. This technology has the potential for development and the prospect of becoming an effective treatment for type I diabetes in the future.

### Disclosure

Authors do not report any disclosures.

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