

## **Pancreatic Islet Transplantation.**

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Justyna Gołębiewska<sup>1</sup>, Piotr Witkowski<sup>2</sup>, Alicja Dębska-Ślizień<sup>1</sup>

<sup>1</sup>Department of Nephrology, Transplant and Internal Medicine, Medical University of Gdańsk, Gdańsk, Poland

<sup>2</sup>Department of Surgery, Transplant Institute, University of Chicago, Chicago, IL, USA

Correspondence address: Justyna Gołębiewska, Department of Nephrology, Transplantology and Internal Medicine, Medical University of Gdańsk, Dębinki 7 Street, 80-952 Gdańsk, cell. + 58 349 25 58, fax. + 58 349 25 51, e-mail: [jgolebiewska@gumed.edu.pl](mailto:jgolebiewska@gumed.edu.pl)

### **Summary**

Patients with type 1 diabetes mellitus who experience life-threatening episodes of severe hypoglycemia despite optimized conservative treatment, may benefit from β-cell transplantation. Pancreatic islet transplantation eliminates hypoglycemic episodes / unawareness, facilitates normalization of glycosylated hemoglobin (HbA1c), and slows down the progression of microvascular complications in patients with unstable diabetes. The first attempt to transplant β-cells, current indications, contraindications, expected benefits, and possible complications of pancreatic islet transplantation together with available methods to monitor transplanted β-cell function are discussed below.

### **Abstract**

Patients with brittle type 1 diabetes who continue to experience life threatening hypoglycemia despite maximal medical management can benefit from β-cell replacement. Islet transplantation eliminates hypoglycemic episodes / unawareness, facilitates normalization of hemoglobin A1c (HbA1c) and decreases microvascular disease progression in patients with labile diabetes. In this article, we review the first attempt of β-cell replacement, current indications, contraindications, expected benefits, and possible complications of pancreatic islet transplantation together with the available techniques that assess the transplanted β-cell function.

### **Introduction**

The pancreas is just a 100-gram organ that has an extrinsic and exocrine function. 85% of pancreatic mass are pancreatic juice producing vesicles, among which there are irregularly scattered endocrine cell clusters, i.e. pancreatic islets. The pancreatic islets were first identified in 1869 by the German pathologist Paul Langerhans. Each islet is built like a miniature organ, has its own specific structure, consists of about two and a half thousand highly specialized cells secreting glucagon (cells A), insulin (B cells), somatostatin (D cells) and pancreatic polypeptide (PP cells), has its own blood vessels and innervation. Glucagon-producing α cells and insulin producing β-cells are the most prominent cells among the endocrine pancreatic cells. These cells co-operate closely, continuously monitoring the level of glucose in the blood and

continuously secrete the appropriate amounts of glucagon and insulin, thus maintaining the concentration of glucose in a narrow physiological range.

In type 1 diabetes, the immune system of the patient irreversibly destroys  $\beta$  cells, which are the only source of insulin in the human body. Insulin, is a vital hormone necessary for proper regulation of blood glucose and tissue utilization of glucose. In this situation, the survival of a patient with type 1 diabetes is possible only due to the administration of exogenous insulin, most often by subcutaneous injections. The course of type 1 diabetes depends on the rate of  $\beta$  cell loss. The depletion of  $\beta$ -cell secretory reserves is the reason for the unsteadiness course of diabetes with a tendency for blood glucose to drastically fluctuate from hyperglycemia to a hypoglycemic coma. Despite the ongoing insulin supplementation, even with the use of modern insulin pumps, the glycemic values in these patients often fluctuate in a very wide range and are far from those observed in the presence of functioning pancreatic islets. The unsteady course of diabetes accelerates the development of chronic complications.

### **Historical overview**

Due to the pitfalls of insulin therapy, attempts have been made to transplant the whole pancreas [1]. Without modern immunosuppression that could prevent rejection, they were doomed to failure as well as attempts to transplant other organs. Only in the 1960s, thanks to the use of azathioprine and glucocorticoids, the first successful pancreatic transplantation was performed. Despite continuous improvement of surgical methods, pancreatic transplantation is a difficult surgical procedure, with an increased risk of perioperative complications.

Therefore, from the beginning of the development of clinical transplantation attempts have been made to isolate and transplant the pancreatic islets themselves. The first isolation of pancreatic islets from the guinea pig pancreas was carried out by a Polish histologist, Prof. Stanisław Moskalewski in 1965 [2, 3]. This method was further improved and described by Paul Lacy [4]. He was the first to transplant islets in rats and then in monkeys and showed it could be an effective method of controlling glycaemia *in vivo* [5, 6]. The first transplantation of pancreatic islets took place in 1974 [7], but by the end of the 20th century the results were unsatisfactory. It was not until 1990 that the first patient with type 1 diabetes completely discontinued insulin after transplantation [8]. In the 80s and 90s, the method of transplantation was improved, but only 8% of patients in the first year could completely discontinue insulin [2]. The breakthrough came in 2000, when the Edmonton team introduced a less diabetogenic, glucocorticoid-free immunosuppressive regimen and used two or three repeated islet transplants from subsequent donors to the same recipient [2, 9]. This time, 100% of patients (7/7) did not require insulin after the first year, compared to the 8% that was noted previously. Unfortunately, in the long-term it turned out that the islets were gradually losing their activity and only 8% of patients did not require insulin 5 years after transplant [10, 11, 12]. Despite this, the majority of patients (around 90%) still had no problems with glycemic control and had no episodes of severe hypoglycemia. In these patients, the presence of c-peptide in the blood was still present, indicating that a number of islets continued to function, preventing the patient from having significant fluctuations in blood glucose. However, they required taking insulin, but much less than before the procedure [10]. In Poland, the first transplantation of pancreatic islets was performed in May 2008 by the Department of General and Transplant Surgery at Warsaw Medical University.

## **Procedure**

In patients with type 1 diabetes, we perform allogeneic transplantation of pancreatic islets isolated from the pancreas of the deceased donor, in three possible variants:

- 1) transplantation of pancreatic islets (ITA - Islets Transplant Alone),
- 2) pancreatic islet transplantation with kidney transplantation (SIKTx - Simultaneous Islets Kidney Transplantation),
- 3) transplantation of pancreatic islets after kidney transplantation (IAK - Islets After Kidney Transplantation)

It is worth mentioning that pancreatic autotransplantation is also performed in patients undergoing complete pancreatectomy due to non-treatable pain in the course of chronic pancreatitis. This operation makes it possible to remove the fibrotic pancreas, and the infusion of isolated islets, even if it does not always provide insulin dependence, it protects against the unstable course of diabetes and episodes of severe hypoglycemia. A thorough discussion of this procedure goes beyond the scope of this article.

The pancreatic islet transplantation itself involves the infusion of pancreatic islets suspended in fluid containing human albumin and heparin into the portal vein of the patient. The portal vein catheter is inserted transcutaneously, then transfused under local anesthesia under USG and fluoroscopy or during mini laparotomy under general anesthesia through the branches of the colon veins. During the infusion, the islets migrate to the liver, where they settle, build into the liver tissue and undertake an endocrine function. In order to minimize the risk of portal vein thrombosis, the pancreatic islets are cleared of exocrine tissue so that the total volume of the transplanted tissue is not greater than 12ml.

In addition, pressure in the portal system is monitored during the procedure. An increase in pressure above 20mmHg or a double increase in pressure in the portal vein in relation to the initial value causes the necessity to suspend the supply of islets and wait until normalization of pressure. In patients without liver disease, there is practically no such high pressure rise during infusion of allogeneic islets, even when it is a 3rd or 4th transplant. The risk is much greater during the infusion of autologous islets, especially when the volume of the islet tissue is greater than 20ml.

Intrahepatic islet transplantation is by far the most optimal place for their implantation. Intrahepatic islet transplantation is associated with maintaining insulin secretion to the liver, which ensures first-pass effect and thus prevents hyperinsulinemia. At the same time, the pulsatile nature of insulin secretion is maintained, which has a beneficial effect on the inhibition of hepatic glucose production [13]. It is also possible to give islets to the intestine, spleen, kidney and peritoneal cavity, but these methods are rarely used, due to their limited effectiveness [14]. Even though being the most effective, the specimen administration also has its drawbacks. Immediately after infusion of the islets into the portal vein blood stream, the inflammatory process activates with the activation of platelets and leukocytes, which leads to damage to a significant number of islets, even as high as 50% [15]. Immediately after the infusion, an increase in transaminase activity to approximately 200 IU / ml is usually observed, which is normalized within 2 weeks. At this time, patients receive prophylactically low-molecular-weight heparin subcutaneously.

## **Indications ITx**

In the absence of other methods of causal treatment of diabetes, both pancreas and pancreatic

islet transplantation remain the only methods to restore the physiological secretion of endogenous insulin. All other treatment options proposed for people with diabetes are limited to regulating plasma glucose. The longer the diabetes lasts, the greater the risk of seizures or unconscious hypoglycemia [16, 17]. The physiological symptoms associated with lowering blood glucose, such as hunger, tachycardia, agitation, which would stimulate the patient to eat a meal or drink a sweet liquid disappears. In this situation, the glucose level drops even lower, often below 50-60mg%, which causes symptoms associated with hypoglycemia in the central nervous system. The patient suddenly experiences disturbances of consciousness, often loses logical contact with the environment, there are qualitative or quantitative disturbances of consciousness, convulsions may appear.

The patient usually requires the help of third parties, oral glucose or glucagon injection. If such an incidence occurs during sleep, it can be the cause of death. Hypoglycemia attacks occur despite the most optimal insulin therapy, the use of pumps, subcutaneous measuring and alarming sensors with low glucose levels.

Hence, the indications for performing islet transplantation (ITA - Islets Transplant Alone) are type 1 diabetes mellitus without accompanying renal failure accompanied by frequent, severe episodes of hypoglycemia, without prodromal symptoms with a threshold of hypoglycemia below 50 mg / dl (risk of lethal neuroglycopenia), unstable course of diabetes despite attempts to modify treatment, poor metabolic control, recurrent ketoacidosis or large emotional problems associated with exogenous insulin therapy [17].

Pancreatic islet transplantation with kidney transplantation (SIKTx - Simultaneous Islets Kidney Transplantation) is performed in patients with type 1 diabetes and end-stage renal disease, renal replacement therapy, but also as a pre-emptive transplant.

On the other hand, transplantation of islets after kidney transplantation (IAK - Islets After Kidney Transplantation) is performed to prevent the progression of diabetic complications and recurrence of diabetic nephropathy in a transplanted kidney.

In particular, the last two variants seem to be the optimal form of treatment, because pancreatic islet transplantation is performed in patients who already receive immunosuppressive treatment against rejection of the transplanted kidney.

The main contraindication for pancreatic islet transplantation is the patient's high body mass and high insulin resistance, because in such situations the effectiveness of the procedure is significantly reduced. The result of transplantation depends on the greatest extent on the number and quality of isolated pancreatic islets obtained per kilogram of body weight. Based on the observation, it has been established that the desired amount that has a chance of a functional effect is at least 5,000 IEQ / kg bw (island equivalents)). Of the one million islets that are on average found in the pancreas, it is usually possible to isolate about 300-500 thousand IEQ. Of the isolated islets, ultimately, less than half survive and produce insulin. Thus, in most patients there is a need to perform sequential transplants. Detailed indications and contraindications for pancreatic islet transplantation are presented in Table 1.

### **Patient Evaluation**

The procedure of reporting the patient to pancreatic islet transplantation is similar to that of kidney transplantation. Patients who meet the qualification criteria and do not meet the criteria for disqualification, based on the general state assessment, cardiovascular efficiency and exclusion of infections and cancers, are placed on the National Waiting List. The patient's registration and qualification is formally carried out by the Transplant Registries of the Ministry

of Health (<https://rejestrytx.gov.pl/tx/>). Patients are put on the waiting list by the physician from the islet transplant center. The recipient receives pancreatic islets from a donor with a consistent blood group. In the case of a waiting queue, priority is given to patients with an unnamed primary blood group and the smallest possible number of incompatible HLA antigens. Prior to the transplantation procedure, a cross-fertilization test is performed with the use of serological techniques. The source of lymphocytes for the cross-fertilization are from the lymph nodes of the deceased donor, which are exposed to the sera of potential recipients from the waiting list. Only recipients whose cross-check is negative, i.e. no cytotoxic antibodies against donor HLA antigens are considered. Transplantation occurs only when the appropriate amount and quality of pancreatic islets are obtained as a result of isolation. Similar to patients awaiting transplantation of a deceased kidney, the PRA-CDC (panel-reactive antibodies) test and the determination of anti-HLA antibodies in a solid phase assay are performed cyclically to assess the degree of immunization.

### **Possible complications**

Complications in the early period after transplantation of the pancreatic islets is rare and does not exceed 10% of all patients. The most common complication is bleeding from or into the liver (4%) and portal vein thrombosis (3%). Portal vein thrombosis occurs rarely, usually in sections, in the small branches of the portal vein and is not clinically significant and disappears without clinical consequences after anticoagulant therapy. Later complications are mainly associated with immunosuppressive therapy. Possible complications are shown in Table 2.

### **Transplantation procedure**

Pancreas transplantation is a vast surgical procedure, performed under general anesthesia, which requires, in addition to vascular anastomoses, anastomosis of the donor duodenum with the intestine or bladder of the recipient in order to drain the pancreatic juice. About 10-15% of recipients lose a pancreas transplant due to portal vein thrombosis in a short time after surgery. Another 15-20% of patients may require surgery again due to bleeding, abscess or other complications. Mortality in the first year after surgery is a low. In the case of successful surgery, it is effective in the majority of patients. Patients do not require insulin immediately after surgery. Despite the risk of complications described above, 5 years after transplantation, 50-60% of patients still have the graft function and patients do not require exogenous insulin. However, due to the risk of complications, pancreatic transplantation is used only in a selected group of patients with type 1 diabetes and sporadically in patients with type 2 diabetes. In Poland, this method of treatment is mainly recommended for patients with type 1 diabetes and end-stage renal failure requiring renal replacement therapy. In this case, the kidneys and pancreas are transplanted simultaneously. The pancreas can also be transplanted sometime after kidney transplantation. The second group is patients with normal renal function, whose daily life is drastically impaired due to unstable diabetes, despite the use of optimal insulin therapy.

Islet transplantation is a minimally invasive alternative to whole pancreas transplantation and is a safe, non-aggravating method of surgical treatment. Such a procedure is a much easier procedure and has a smaller number of complications, but also gives a smaller chance of achieving insulin dependence. It seems that both methods, i.e. pancreas transplantation and transplantation of isolated pancreatic islets should be treated as complementary methods. In the case of failure of pancreas transplantation, the patient may be offered the next transplantation of islets, and the patient with transplanted islet insufficiency - pancreatic transplantation.

### **Metabolic effects and influence on late complications of diabetes**

Transplantation of pancreatic islets to the liver via the portal vein is a safe method, but the metabolic results are currently worse than in the case of whole pancreas transplantation. The results of transplantation depend on the quantity and quality of the transplanted islets and on the immunosuppressive treatment used, as well as therapy reducing intravascular coagulation or non-specific inflammation. The final result of the transplantation can be assessed only a few weeks after the surgery, because the pancreatic islets need time to rebuild the vascular system. Only then are they able to properly produce insulin, glucagon and other peptides in response to stimulus and blood glucose levels. Currently, when stronger immunosuppressant drugs are used than those proposed by the Edmonton center 13 years ago, the results of islet transplantation are much better than those published in 2005. Not just 8%, but 50-60% of patients do not require insulin administration 5 years after the procedure. It should be emphasized that achieving insulin independence is not the main goal of pancreatic islet transplantation. The main goal, is to achieve a stable course of the disease with glycosylated hemoglobin below 7%, with the concentration of fasting c-peptide above 0.3ng / ml, which effectively eliminates life-threatening hypoglycemic states. This is reflected in the Igls classification used to assess the function of transplanted pancreatic islets, resulting from the consensus of experts established in January 2017 at the 1st IPITA / EPITA Opinion Leaders Workshop in Igls, Austria (Table 3) [18]. Currently, the decisive factor determining the effective therapy of diabetic patients is the assessment of glycosylated hemoglobin below 6.5%. Restoration of endogenous insulin secretion after islet transplantation has a beneficial effect on lipid disorders, and preserved secretion of c-peptide, even in the absence of full insulin dependence, definitely inhibiting the development of secondary diabetes complications: reduces the incidence of life-threatening hypoglycemia, inhibits the development of nephropathy, retinopathy and diabetic enteropathy [19]. Even in the case of only residual secretory function of the transplant, patients do not have severe, symptomatic hypoglycemia [20].

### **Loss of function**

A significant percentage of patients have a progressive deterioration of the function of transplanted pancreatic islets, even in spite of their initially excellent function. There are two possible proposed mechanisms leading to the destruction of  $\beta$  cells [21]. The first of these is autoaggression, which may occur with an increase in anti-GAD (anti-GAD) and anti-IC (ICA) antibody titers, but may be dominated by a mechanism of cellular cytotoxicity that we can neither monitor nor prevent or stop. The second mechanism is alloaggression, i.e. rejection in both the cellular and humoral mechanisms. Due to considerable technical difficulties in obtaining material for histo-pathological examination, the basis for diagnostics in the search for the cause of the deterioration of island function is the search for autoantibodies and anti-HLA antibodies, including those specific for the donor (DSA). Even if the potential mechanism responsible for the deterioration of islet function is confirmed, treatment options are significantly reduced. A detailed explanation of pathomechanisms of the loss of the function of transplanted islets requires further detailed studies, the consequence of which will probably be an improvement in results.

It is worth noting, patients in the course of a single pancreatic islet transplant eventually receive less than half the number of the healthy person's islets. Therefore, even if insulin dependence is achieved, these patients still have the limit efficiency of  $\beta$  cells and only a small metabolic reserve. If you increase your intake of carbohydrates and / or calories, reduce physical strain or increase your body weight, you may need to re-use your insulin. Decreased insulin sensitivity is compensated by the more and more intense secretion by  $\beta$  cells. It seems that, as in type 2

diabetes, in the case of increased insulin resistance, compensatory hyperinsulinemia leads to exhaustion of the secretory capacity of transplanted  $\beta$  cells. Therefore, even a re-weight reduction does not have to guarantee a return to insulin dependence. According to the "accelerator hypothesis", insulin resistance is considered to be the main causative agent of diabetes, which is supposed to increase the apoptosis of  $\beta$  cells, causing the release of pancreatic antigens and activation of the immune response [22].

### **Monitoring of islet graft function.**

Despite the progress that has been made in isolation and immunosuppressive techniques, progressive loss of function of transplanted islets is observed, as mentioned above, and insulin dependence is limited in time, even despite the good initial function of transplanted  $\beta$  cells. Due to the lack of diagnostic possibilities allowing for the selection of patients in whom it will not be possible to obtain a stable satisfactory function of transplanted pancreatic islets, the monitoring of  $\beta$ -cell function is of key importance. The assessment of the function of pancreatic islets is complicated and reflects the complexity of the process involved in regulating blood glucose. Proper monitoring of  $\beta$ -cell function should include: the glycemic profile, glycemic index assessment, hypoglycemia awareness and functional studies analyzing glucose and c-peptide concentrations after exposure to a standardized insulin stimulatory stimulant such as arginine, glucagon, glucose or mixed meal (Mixed Meal Tolerance Test). The most frequently used to assess the function of transplanted  $\beta$  cells is the beta-score system (Table 4) [23]. The higher the total score, correlates with better pancreatic islet function. In order to calculate the beta-score you need information about the c-peptide value in the 90-minute Mixed Meal Tolerance Test. However substantively justified, conducting such an assessment is particularly burdensome for the patient. Therefore, easier ways to apply this in everyday practice is sought after. The basis for the monitoring of transplantation remains the determination of c-peptide concentration, glycated hemoglobin and glucose concentration. It is also possible to use coefficients based on fasted blood glucose, c-peptide or HbA1c, and data from an interview with daily insulin requirement on a single blood sample. These are: Secretory Unit of Islet Transplant Objects (SUITO) [24], Transplant Estimated Function (TEF) [25], Homeostasis Model Assessment (HOMA) 2-B% [26], coefficient c-peptide / glucose (CP / G), coefficient c-peptide / glucose creatinine (CP / GCr) [27] and BETA-2 score [28]. The authors' experience shows that BETA-2 score and SUITO are particularly useful and valuable in monitoring the function of pancreatic islets [29]. It seems that they may replace more complex functional tests in the future, as the calculation of eGFR significantly reduced the performance of 24-hour urine collection to determine creatinine clearance.

### **Summary:**

Currently, both pancreas and islet transplantation remain the only methods to restore the physiological secretion of endogenous insulin. Transplantation of pancreatic islets, is a minimally invasive alternative to transplantation of the whole pancreas and is a safe, non-intrusive method of treatment. It seems to be the optimal form of management especially in patients with kidney transplants already receiving immunosuppressive treatment to prevent rejection of transplanted kidney.

Despite the progress that has been made in isolation and immunosuppressive techniques, progressive loss of the function of transplanted islets is observed, and insulin dependence is in most cases limited in time, despite the good initial function of transplanted  $\beta$  cells. Therefore, the achievement of non-insulin dependence is not the primary goal of pancreatic islet

transplantation. The main goal, is to stabilize the disease, minimize the risk of secondary complications and eliminate life-threatening episodes of severe hypoglycemia.

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**Table 1. Indications and contraindications for pancreatic islet transplantation**

Indications
Type 1 diabetes lasting ≥5 years with a minimum of one complication: <ul style="list-style-type: none"> <li>• hypoglycemic episodes without preceding symptoms or with symptoms of central nervous system hypoglycemia OR</li> <li>• Metabolic Liability understood as 2 or more episodes of severe hypoglycemia or 2 or more hospitalizations due to ketoacidosis during the year OR</li> <li>• HbA1c &gt; 7% despite intensive insulin therapy</li> <li>• no release of C-peptide (&lt;0.3 ng / mL) on an empty stomach</li> </ul>
Contraindications
Absolute contraindications: <ul style="list-style-type: none"> <li>• If you are a recipient of other organs other than the kidney, except those who have pancreas who have lost the function of a transplanted pancreas.</li> <li>• Unstable or untreated diabetic retinopathy</li> <li>• Active infection, including hepatitis B or C</li> <li>• Invasive Aspergillosis, histoplasmosis, coccidioidomycosis in the last 12 months.</li> <li>• Severe coexisting cardiovascular disease: heart attack over the last 6 months; heart failure with EF &lt;30% ejection fraction,</li> <li>• Creatinine clearance &lt;60 mL / min evaluated on the basis of 24-hour urine collection and / or eGFR CKD-EPI &lt;60 mL / min / 1.73 m<sup>2</sup> (If it is suspected that the assessment of renal function using the above methods may be inadequate indicated there is a more accurate assessment e.g. using DTPA scintigraphy), except for patients with end-stage renal failure qualified to or after renal transplantation.</li> <li>• Cirrhosis, Portal hypertension, Acute pancreatitis, Active peptic ulcer disease</li> <li>• Active cancer or cured cancer before the relevant grace period Dodatni test ciążowy</li> <li>• Positive cross-match</li> <li>• Unstable mental illness, or poorly pharmacologically controlled, inability to cooperate due to diabetic character, Alcoholism or drug addiction</li> <li>• Inability to give informed consent to the procedure</li> </ul>
Relative contraindications: <ul style="list-style-type: none"> <li>• Nicotinism (6-month abstinence required)</li> <li>• Status after amputations of the lower knees, state after stroke</li> <li>• A history of liver disease or current abnormalities in laboratory tests, i.e. ALAT / ASPAT aminotransferase activity &gt; 3 x norm, excluding Gilbert's syndrome.</li> </ul>

**Table 2. Possible complications related to pancreatic islets transplantation.**

1.	The risk of pancreatic islet cells infection: Because pancreatic islet cells undergo a complex processing process, there is a risk that they will be superinfected with bacteria. Since the isolation of pancreatic islets is in accordance with restrictive procedures, the risk of infection is negligible.
2.	Allergy to HLA antigens: In such a case, the availability of organs suitable for transplantation, e.g. the kidney, will be more limited.
3.	Bleeding: It is very rarely necessary to undergo surgery to stop bleeding (1%).
4.	Portal vein thrombosis (3%): The complication of the procedure may be a blood clot in the portal vein that partially or completely closes the flow in the main vein that delivers blood to the liver. This may lead to transient abnormalities in laboratory tests (increase in aminotransferases) or serious complications in the form of liver failure resulting in the necessity of transplantation or death. The risk of thrombus formation is proportional to the number of pancreatic islets given. Therefore, a very small volume, i.e. approx. 10 ml, is used for transplantation and given together with heparin. For the next 7 days, prophylaxis with low molecular weight heparin is carried out.
5.	<b>Damage to the abdominal organs</b> It may involve puncturing the gallbladder, large intestine, hepatic artery or other structures during the pancreatic islet delivery procedure. The provision of complications related to the placement of the catheter in the portal vein may require surgery, but the risk of such complications is low (<5%).
6.	<b>Failure to gain access to the portal vein</b> It may happen that a radiologist for various reasons (e.g. a history of thrombosis), will not be able to puncture the portal system. In this situation, it is possible to transplant the pancreatic islets during the surgery.
7.	<b>Low blood pressure</b> Hypotension which is not related to bleeding but resulting from pancreatic islet transplantation is a rare complication.
8.	<b>Hypoglycemia</b> After transplantation of pancreatic islets, severe hypoglycemia may occur, due to the release of insulin from parts of disintegrating islets
9.	<b>Failure to achieve independence from insulin</b> Even if the pancreatic islet transplant is successful, the patient may still need to take insulin. In this situation, a further transplantation of pancreatic islets, pancreas transplantation is possible, or it may be advisable to continue to take insulin at the modified dose.
10.	<b>Unspecified time of functioning of the transplanted pancreatic islets:</b> Even if the initial function of transplanted islets is good, it is not known how long it will be preserved.
11.	<b>Increased retinopathy</b> During the first year after transplantation of pancreatic islets, the changes of the

nature of retinopathy may intensify. After a year, the changes usually stabilize.

**Table 3. Igls classification for the assessment of the function of transplanted pancreatic islets [18]**

<b>β-cell Graft Functional Status</b>	<b>HbA1c % (mmol/mol)*</b>	<b>Severe hypoglycemic episodes, events per year</b>	<b>Insulin requirements (U/kg/day)</b>	<b>C-peptide</b>	<b>Treatment Success</b>
<b>Optimal</b>	≤6.5 (48)	None	None	> Baseline †	Yes
<b>Good</b>	<7.0 (53)	None	< 50% baseline ‡	> Baseline †	Yes
<b>Marginal</b>	Baseline	< Baseline §	≥ 50% baseline	> Baseline †	No ¶
<b>Failure</b>	Baseline	Baseline **	Initial Output	Baseline ††	No

HbA1c, glycated hemoglobin. Baseline, pre-transplant assessment.

\*Mean glucose should be used to provide an estimate of the HbA1c in the setting of marked anemia or administration of Dapsone [10].

†Should also be >0.5 ng/ml (>0.17 nmol/l) fasting or stimulated.

‡Should also be <0.5 U/kg/day; might include the use of noninsulin anti-hyperglycemic agents.

§Should severe hypoglycemia occur following treatment, then continued benefit may require assessment of hypoglycemia

awareness, exposure to serious hypoglycemia [<54 mg/dl (3.0 mmol/l)], and/or glycemic variability/lability with demonstration of improvement from baseline.

¶Clinically, benefits of maintaining and monitoring b-cell graft function may outweigh risks of maintaining immunosuppression.

\*\*If severe hypoglycemia was not present before b-cell replacement therapy, then a return to baseline measures of glycemic

control used as the indication for treatment (Table 2) may be consistent with b-cell graft failure.

††May not be reliable in uremic patients and/or in those patients with evidence of C-peptide production prior to b-cell replacement therapy.

**Table 4. Beta Score for the assessment of islet graft function.**

	2 points	1 point	0 points
Concentration of glucose on an empty stomach (mg / dL OR mmol / L)	<99 LUB <5.5	100 – 124 LUB 5.6-6.9	>125 LUB >7.0
HbA1c (%)	<6.1	6.2 – 6.9	>7.0
Average Daily Insulin Dose (IU/kg/day)	---	0.01 – 0.24	>0.25
C-peptide concentration (ng/mL) after 90 min Mixed Meal Tolerance Test	>0.9	0.3 – 0.89	<0.3