VIA MEDICA
REVIEW ARTICLE
ISSN 2450–7458

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Beta cell replacement therapy

ABSTRACT

Beta cell replacement therapy is currently the only treatment method that allows restoration of physiological endogenous insulin secretion in the amounts corresponding to the current body requirements. Beta cell replacement options available for highly selected patients with brittle type 1 diabetes include solid-organ pancreas and islet transplantation. Beta cell replacement therapy may be offered to patients with both good kidney function and renal failure. In progressive renal failure, beta cell transplantation may be performed simultaneously with kidney transplantation or afterwards. Islet autotransplantation is offered to patients submitted to total pancreatectomy. In patients with brittle type 1 diabetes who continue to experience life threatening severe hypoglycaemia episodes despite optimized insulin therapy, beta cell replacement helps improve hypoglycaemia awareness, thus reducing the risk of severe hypoglycaemia episodes, facilitates blood glucose control with normalization of haemoglobin A_{1c} (HbA_{1c}) level, and reduces microvascular disease progression. In patients undergoing total pancreatectomy, infusion of the patient's own islets isolated from the removed pancreas prevents blood glucose level excursions and reduces the risk of surgically-induced diabetes. In this article, we review the current indications and contraindications to beta cell replacement, expected benefits, and possible complications of beta cell transplantation. (Clin Diabetol 2020; 9; 5: 344–355)

Key words: solid-organ pancreas transplantation, pancreatic islet transplantation, severe hypoglycaemia, diabetes type 1, total pancreatectomy

Introduction

Due to the lack of other causal treatments for diabetes type 1, both pancreas transplantation and islet transplantation remain the only methods to restore physiological secretion of endogenous insulin. All other therapeutic options offered to patients with diabetes type 1 are limited to attempts to achieve near normoglycaemia using insulin preparations administered subcutaneously.

Beta cell transplantation is a complex therapeutic process including patient selection, i.e., determining indications for and contraindications to the procedure; immunological assessment; evaluation of the technical feasibility of the procedure; donor selection along with procurement, storage, and appropriate preparation of the organ for transplantation; performing the transplantation procedure; and immunosuppressive therapy and monitoring the function of the transplanted organ with constant evaluation of the patient health status. In the case of pancreatic islet transplantation, it is also necessary to perform pancreatic islet isolation to obtain islets that fulfil the qualitative and quantitative criteria to allow their administration to the patient.

The effectiveness of beta cell transplantation is usually limited in time, and the availability of this method for patients is limited by possible complications

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Clinical Diabetology 2020, 9; 5: 344–355
DOI: 10.5603/DK.2020.0035
Received: 26.03.2020 Accepted: 12.06.2020

of more or less invasive procedures and the need for immunosuppressive therapy. However, it is a valuable treatment option which may significantly improve patients' quality of life, delay development of chronic complications, or even prolong life in carefully selected patients in whom the expected benefits and risks were appropriately weighted.

Available forms of beta cell transplantation

In clinical practice, the available forms of beta cell transplantation offered to patients with diabetes type 1 include transplantation of the whole pancreas procured from a deceased donor and transplantation of pancreatic islets isolated from a pancreas procured from a deceased donor. Both these procedures may be performed in three variants:

1. pancreas transplantation alone (PTA)/islet transplantation alone (ITA);
2. simultaneous pancreas and kidney (SPK) transplantation/simultaneous islet and kidney transplantation (SIKTx);
3. pancreas after kidney (PAK) transplantation/islets after kidney (IAK) transplantation.

The most commonly offered solution is a simultaneous transplantation of a pancreas and a kidney procured from the same deceased donor, performed in patients with diabetes type 1 who developed end-stage renal disease requiring chronic renal replacement therapy due to diabetic nephropathy. Simultaneous pancreas and kidney transplantation may also be pre-emptive i.e., in patients with end-stage renal disease but before dialysis treatment is commenced. The second most common procedure is pancreas transplantation in a patient after earlier kidney transplantation from a deceased or living donor. Other treatment options are employed much less often. According to the data from the International Pancreas Transplant Registry (IPTR), a total of 11,104 pancreas transplantation procedures were performed worldwide in 2005–2014, including 74% of simultaneous kidney and pancreas transplantations, 17% of pancreas after kidney transplantations and 9% of pancreas transplants alone [1]. According to the Poltransplant data, 20 kidney and pancreas transplantation or pancreas transplantation alone procedures were performed in Poland in 2018. The transplantation waiting list in our country includes approximately 50 patients (including 10 awaiting pancreas transplantation alone) [2]. Attempts to transplant a pancreas fragment retrieved from a living donor have also been reported but this is not a routine procedure and it is not performed in Poland.

According to the Collaborative Islet Transplant Registry (CITR), a total of 2150 pancreatic islet transplantations involving 2619 donors and 1086 recipients were performed worldwide in 1999–2015 [3].

Centres performing beta cell transplantation procedures in Poland are listed in Table 1.

Indications for pancreas and pancreatic islet transplantation

The rationale for simultaneous pancreas or pancreatic islet transplantation and kidney transplantation, and pancreas or pancreatic islet transplantation in patients with a functioning transplanted kidney is to improve long-term outcomes compared to kidney transplantation alone. The prognosis is improved by a positive effect of long-term normoglycaemia, preventing the development of chronic micro- and macroangiopathic complications [4–10].

Indications for beta cell transplantation, either as the solid-organ pancreas or isolated pancreatic islets, in the remaining cases, i.e., in patients with diabetes type 1 and functioning native kidneys, have been summarized in the 2018 International Pancreas and Islets Transplant Association/European Pancreas and Islets Transplant Association (IPITA/EPITA) guidelines. Indications for beta cell transplantation include at least one documented severe hypoglycaemia episode during the preceding year, the proportion of time with low blood glucose levels (< 54 mg/dL) ≥ 5% during continuous glucose monitoring (CGM) or hypoglycaemia unawareness along with indicators of poor metabolic control (haemoglobin A_{1c} [HbA_{1c}] level > 7.5–8.0%) or excessive blood glucose excursions, such as the CGM coefficient of variation ≥ 30% or standard deviation of blood glucose levels during CGM ≥ 40 mg/dL [11]. Another indication for pancreas or pancreatic islet transplantation alone in patients with good renal function are recurrent episodes of ketoacidosis despite individually optimized insulin treatment. Beta cell transplantation is associated with the need for immunosuppressive treatment for the duration of functioning of the transplanted pancreas/pancreatic islets. Thus, simultaneous beta cell and kidney transplantation or beta cell transplantation alone as either the solid-organ pancreas or isolated pancreatic islets in patients after earlier transplantation of a kidney or another vascularized organ (lung, heart) seems the optimal approach as beta cell transplantation in such cases is performed in patients receiving immunosuppressive therapy to prevent rejection of the other transplanted organ. In these patients, indications for beta cell transplantation are somewhat less rigorous compared to patients with diabetes type 1 and a good function of native kidneys.

Table 1. Pancreas and pancreatic islet transplantation centres in Poland

Pancreatic islet transplantation — GDAŃSK
Klinika Chirurgii Ogólnej, Endokrynologicznej i Transplantacyjnej Uniwersyteckie Centrum Kliniczne w Gdańsku, Centrum Medycyny Inwazyjnej ul. Smoluchowskiego 17, 80–210 Gdańsk phone: 58 349 30 10 fax: 58 349 30 50 e-mail: ichir@gumed.edu.pl
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Contraindications to pancreas and pancreatic islet transplantation

When selecting patients for pancreas or pancreatic islet transplantation, it is necessary to consider contraindications to both the procedure itself and long-term immunosuppressive treatment. Absolute contraindications are the same and include a malignancy (with a waiting period post successful treatment), persistent untreated infection, severe irreversible systemic disease with limited life expectancy, and lack of patient compliance, e.g., due to alcohol abuse, drug addiction, or a mental disorder. A large body mass is also a contraindication to beta cell transplantation. In case of pancreas transplantation, obesity is associated with an increased risk of postoperative complications including thrombosis, infection, and pancreatic graft inflammation. In the case of pancreatic islet transplantation, large body mass is usually associated with high insulin resistance which significantly limits the effectiveness of the procedure.

Table 2. Indications for and contraindications to pancreatic islet transplantation in patients with diabetes type 1 and normal native kidney function

Indications
Diabetes type 1 with at least one of the following complications: • At least one documented episode of severe hypoglycaemia (requiring the help of other persons) during the preceding year • Proportion of low blood glucose levels (< 54 mg/dL) during CGM ≥ 5% • Hypoglycaemia unawareness with Gold score ≥ 5 • Metabolic lability defined as at least 2 hospitalizations per year due to ketoacidosis Along with indicators of poor metabolic control: • HbA_{1c} level > 7.5–8.0% • CGM coefficient of variation ≥ 30% or • Standard deviation of blood glucose levels during CGM ≥ 40 mg/dL
Contraindications
Absolute contraindications: • Unstable or untreated proliferative diabetic retinopathy • Active infection, including viral hepatitis B or C • Invasive aspergillosis, histoplasmosis, or coccidioidomycosis within last 12 months • Severe concomitant cardiovascular disease: myocardial infarction within last 6 months, heart failure with left ventricular ejection fraction < 30% • Creatinine clearance < 50 mL/min based on 24-hour urine collection and/or eGFR (CKD-EPI equation) < 50 mL/min/1.73 m^2 (If evaluation of renal function using these methods is suspected to be inadequate, more precise evaluation may be indicated, e.g., using DTPA scintigraphy), except for patients with end-stage renal failure scheduled for or after previous kidney transplantation • Cirrhosis • Portal hypertension • Acute pancreatitis • Active malignancy or cured malignancy before the end of appropriate waiting period • Positive pregnancy test • Positive cross-match test • Alcohol or drug abuse • Unstable mental disorder or mental disorder not controlled by medications, lack of compliance due to mental status changes related to diabetes • Inability to provide informed consent **Relative contraindications:** • Smoking (6-month abstinence is required) • Active peptic ulcer disease • A history of liver disease or abnormal liver function tests, i.e., aminotransferase (ALT/AST) activity > 3 × upper limit of normal values, except for Gilbert syndrome

ALT — alanine transaminase; AST — aspartate transaminase; CGM — continuous glucose monitoring; CKD-EPI — Chronic Kidney Disease Epidemiology Collaboration; DTPA — diethylenetriamine pentaacetic acid; eGFR — estimated glomerular filtration rate; HbA_{1c} — haemoglobin A_{1c}

Other contraindications to pancreas transplantation include advanced atherosclerotic iliac artery disease which precludes the procedure and general contraindications to a major surgery, such as severe coronary artery disease or heart failure.

Contraindications to pancreatic islet transplantation, in addition to insulin resistance with the mean daily insulin requirement of > 1 unit/kg body mass, include cirrhosis, active liver disease with the evidence of liver damage, portal hypertension, and renal failure. In patients with progressive chronic kidney disease with the estimated glomerular filtration rate (GFR) between 30 and 50 mL/min/1.73 m^2, simultaneous kidney and pancreatic islet transplantation should be considered, or beta cell transplantation should be postponed until after kidney transplantation.

Detailed indications for and contraindications to pancreatic islet transplantation in various clinical scenarios are shown in Tables 2, 3 and in Figure 1 A, B.

Pancreas transplantation procedure

Pancreas transplantation is a major surgery performed under general anaesthesia which requires, in addition to vascular anastomoses, anastomosing the duodenum of the donor with the intestine or the urinary bladder of the recipient for pancreatic juice drainage. The pancreas is transplanted heterotopically. Before transplantation, the vascular supply of

Table 3. Indications for and contraindications to pancreatic islet transplantation in patients with diabetes type 1 after kidney or other vascularized organ transplantation

Indications
Diabetes type 1 with at least one of the following complications:
• At least one documented episode of severe hypoglycaemia (requiring the help of other persons) during the preceding year
• Proportion of low blood glucose levels (< 54 mg/dL) during CGM ≥ 5%
• Hypoglycaemia unawareness with Gold score ≥ 5
• Metabolic lability defined as at least 2 hospitalizations per year due to ketoacidosis
OR with indicators of poor metabolic control:
• HbA_{1c} level > 7.5–8.0%
• CGM coefficient of variation ≥ 30% or
• Standard deviation of blood glucose levels during CGM ≥ 40 mg/dL
Contraindications
Absolute contraindications:
• Unstable or untreated proliferative diabetic retinopathy
• Active infection, including viral hepatitis B or C
• Invasive aspergillosis, histoplasmosis, or coccidioidomycosis within last 12 months
• Severe concomitant cardiovascular disease: myocardial infarction within last 6 months, heart failure with left ventricular ejection fraction < 30%
• Cirrhosis
• Portal hypertension
• Acute pancreatitis
• Active malignancy or cured malignancy before the end of appropriate waiting period
• Positive pregnancy test
• Positive cross-match test
• Alcohol or drug abuse
• Unstable mental disorder or mental disorder not controlled by medications, lack of compliance due to mental status changes related to diabetes
• Inability to provide informed consent
Relative contraindications:
• Smoking (6-month abstinence is required)
• Active peptic ulcer disease
• A history of liver disease or abnormal liver function tests, i.e., aminotransferase (ALT/AST) activity > 3 × upper limit of normal values, except for Gilbert syndrome
Specific contraindications in vascularized organ recipients:
• Advanced failure of the transplanted organ, including patients awaiting retransplantation
• Polyoma BK virus infection in kidney graft recipients
• Current complications of immunosuppressive therapy precluding its transient intensification

ALT — alanine transaminase; AST — aspartate transaminase; CGM — continuous glucose monitoring; HbA_{1c} — haemoglobin A_{1c}

the pancreas is reconstructed by anastomosing the superior mesenteric artery and the splenic artery of the procured pancreas with an Y-graft from the iliac artery of the recipient. Venous outflow is provided by the portal vein of the harvested pancreas which is anastomosed with the inferior vena cava or the iliac vein of the recipient. A much less commonly employed option is an anastomosis with the portal circulation of the recipient. The common iliac artery of the donor is anastomosed end-to-side with the external iliac artery of the recipient, and the pancreatic juice is drained by anastomosing the duodenum of the donor mostly with the small intestine of the recipient. A duodeno-duodenal anastomosis is rarely performed. A duodenal-bladder anastomosis has become obsolete due to high complication rates.

Possible complications after pancreas transplantation

Pancreas transplantation is a technically challenging procedure with relatively high complication rates, leading to a loss of the transplanted organ in about

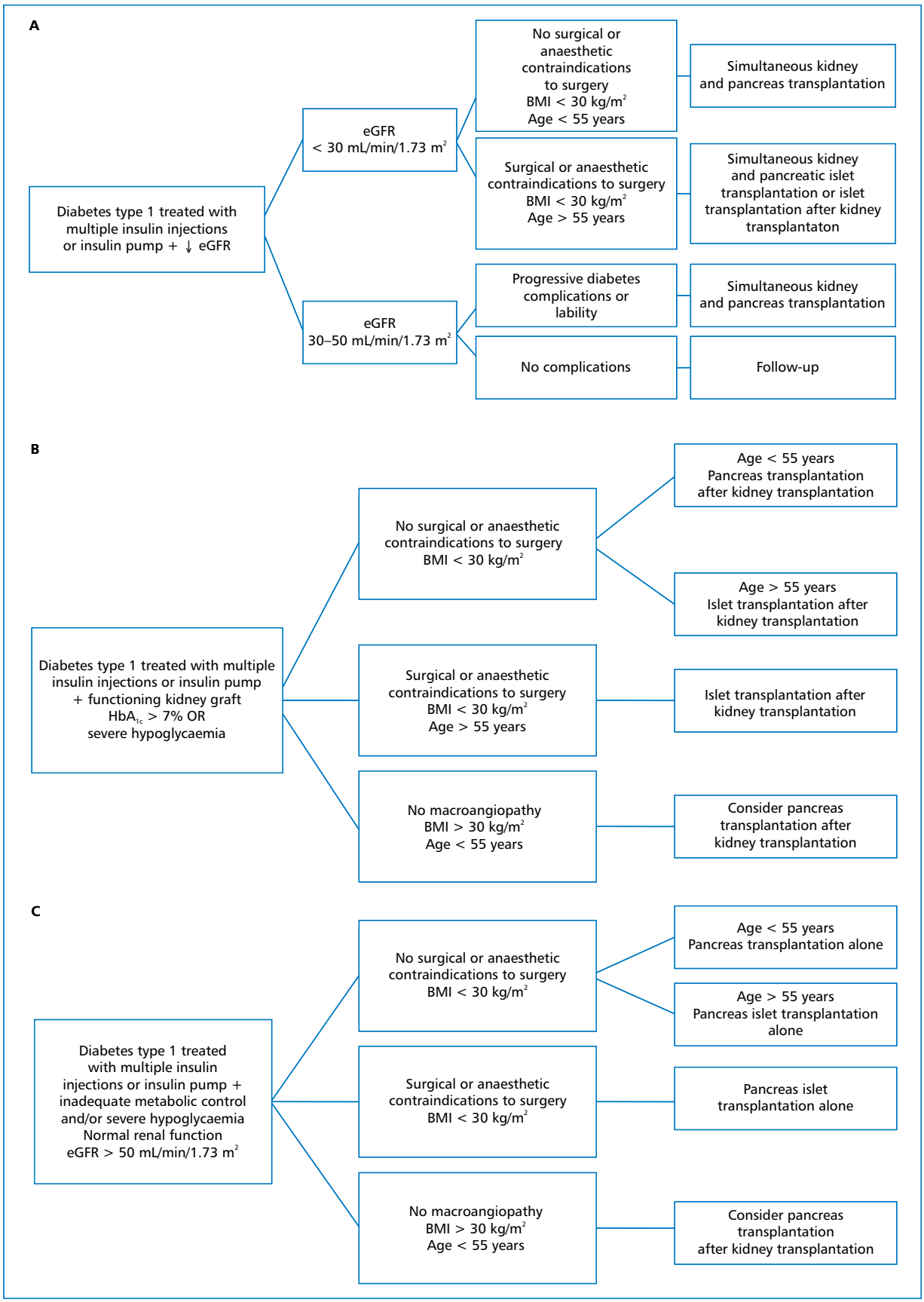

Figure 1. Indications for pancreas/pancreatic islet transplantation in selected clinical settings according to Wojtusciszyn et al. [17]. BMI — body mass index; eGFR — estimated glomerular filtration rate; HbA_{1c} — haemoglobin A_{1c}

10% of cases. Another 15–20% of patients require reoperation due to bleeding, abscess or other complications. Mortality during the initial year after the procedure is several percent. The postoperative course is largely dependent on the appropriate donor and recipient selection. Pancreas graft vessel thrombosis (accounting for about 10–20% of the postoperative complications) manifests within the first week in 70% of patients and usually necessitates removal of the transplanted pancreas. It is the most common early cause of graft loss. Venous thrombosis is nearly twice more common than arterial thrombosis. Intraabdominal infection is the second most common complication. The most common pathogens are staphylococci, and the most common fungal pathogen is *Candida albicans*. Intraabdominal fungal infections are particularly dangerous and associated with an increased postoperative mortality. Mild, self-limiting graft pancreatitis is nearly universal due to transplant-related ischaemic injury. It may last for 3–4 weeks after the surgery. It manifests with pain in the graft area, fever, nausea, vomiting, and elevated inflammatory markers, while elevated amylase and lipase activity is not a universal finding. Inflammation may lead to necrosis and the development of peripancreatic abscesses, fistulae, or pancreatic pseudocysts. Intestinal fistula usually develops with 3 months after the transplantation. It manifests as an acute abdomen and most patients require urgent surgery. Other possible complications include intraperitoneal or gastrointestinal bleeding from the pancreas or a leaking vascular anastomosis.

Pancreatic islet transplantation

Pancreatic islet transplantation involves infusion of pancreatic islets suspended in a solution containing human albumin and heparin to the portal vein of the patient. The portal vein is cannulated percutaneously and transhepatically under ultrasonographic and fluoroscopic guidance with local anaesthesia, or via colic vein branches by minilaparotomy under general anaesthesia. During the infusion, pancreatic islets migrate to the liver where they engraft in the hepatic tissue and exert their endocrine function. To minimize the risk of portal vein thrombosis, pancreatic islets are separated from the exocrine tissue so that the total pellet volume does not exceed 12 mL.

In addition, pressure in the portal system is monitored during the procedure. A portal vein pressure increase above 20 mm Hg or a twofold increase compared to the baseline values necessitates temporary interruption of the infusion until the pressure normalizes. In patients without liver disease, such pressure the increase is virtually never observed during the infusion of allogenic islets, even during the third or fourth transplantation procedure. The risk is much higher during the infusion of autologous islets, particularly if the islet tissue volume exceeds 20 mL.

Until now, intrahepatic islet transplantation is the most optimal implantation site. Intrahepatic islet transplantation is associated with the preservation of insulin secretion to the liver which allows for the first pass effect and thus prevents hyperinsulinemia. At the same time, the pulsating nature of insulin secretion is preserved which has a beneficial effect on inhibiting hepatic glucose synthesis [12]. It is also possible to administer pancreatic islets to the intestine, spleen, renal capsule, and the peritoneal cavity but these approaches are rarely used due to their limited efficacy [13]. Although most effective, intrahepatic islet administration also has some downsides. Immediately after islet infusion to the portal vein bloodstream, an inflammatory process is triggered with platelet and leukocyte activation, leading to damage to significant proportion of islets, up to 50% [14]. Directly after the infusion, an elevation of transaminase activity to about 200 IU/mL is observed, with normalization within 2 weeks. During this time, the patients are prophylactically administered low-molecular-weight heparin subcutaneously.

Possible complications after pancreatic islet transplantation

Complications in the early period following pancreatic islet transplantation are rare, occurring in up to 10% of patients. The most common complications are bleeding from or into the liver (4%) and portal vein branch thrombosis (3%). Portal vein thrombosis occurs rarely, usually segmentally in small portal system branches, has no clinical significance and typically resolves with anticoagulation without clinical sequelae, although it may theoretically lead to severe complications, with hepatic failure requiring liver transplantation or leading to death. In the later period, complications are mostly related to the immunosuppressive treatment. Possible complications are listed in Table 4.

Pancreatic islet transplantation *vs.* pancreas transplantation

Pancreas transplantation is a major surgery performed under general anaesthesia. About 10% of the recipients lose the graft shortly after the surgery, most commonly due to graft portal vein thrombosis. If the procedure is successful, patients do not require insulin immediately after the surgery, and 50–60% of patients continue to have preserved graft function and do not require exogenous insulin at 5 years after the transplantation. However, due to the extent of the surgery and the risk of postoperative complications,

Table 4. Possible complications associated with pancreatic islet transplantation

1. Risk of pancreatic islet cell infection
   As pancreatic islet cells undergo complex processing, there is a risk of bacterial infection during their isolation. There is also a risk of infection with donor's bacteria. The risk of both is negligible as pancreatic islet isolation is performed in accordance to very restrictive procedures
2. Sensitivity to HLA antigens
   In such case, the organ availability for transplantation (e.g., kidney) will be more limited
3. Bleeding
   In very rare cases, a surgery is necessary to stop bleeding (1%)
4. Portal vein thrombosis (3%)
   A complication of the procedure may be portal vein thrombosis resulting in partial or complete blood flow obstruction. This may frequently lead to transient laboratory test abnormalities (elevated transaminases) or very rarely to serious complications of liver failure. The risk of thrombosis is proportional to the amount of infused pancreatic islets. For this reason, only a very small volume (about 10 mL) is administered with heparin during the transplantation, and the procedure is followed by low-molecular-weight heparin prophylaxis for 14 days
5. Abdominal organ damage
   This may include a puncture of the gall bladder, large intestine, hepatic artery or other structures when infusing pancreatic islets Treatment of complications related to catheter placement in the portal vein may require surgery but the risk of such complications is small (< 5%)
6. Failure to achieve access to the portal vein
   For various reasons (e.g., previous thrombosis), the interventional radiologist may be unable to achieve access to the portal system. In such a situation, surgical islet transplantation is possible
7. Low blood pressure
   A rare complication is hypotension unrelated to bleeding, secondary to islet transplantation itself
8. Hypoglycaemia
   Severe hypoglycaemia may develop following islet transplantion due to insulin release from damaged islets
9. Failure to achieve non-insulin dependence
   Even if pancreatic islet transplantation is successful, the patient may still require insulin. In such a situation, options include another islet transplantation, solid-organ pancreas transplantation, or continuation of insulin therapy with appropriate dosing adjustment
10. Undetermined duration of transplanted islet function
    Even if baseline function of the transplanted islets is good, the duration of their functioning is unpredictable
11. Worsening of retinopathy
    The worsening of retinopathy may occur during the first year after pancreatic islet transplantation. These changes usually become stabilized beyond the first year

HLA — human leukocyte antigen

pancreas transplantation may only be performed in a small group of patients. In these patients, simultaneous kidney and pancreas transplantation is associated with a survival benefit compared to kidney transplantation alone, with the 10-year survival of 67% in simultaneous kidney and pancreas transplant recipients compared to 56% and 36% in kidney transplant recipients from a living or deceased donor, respectively [1, 15]. All-cause mortality in simultaneous kidney and pancreas transplant recipients was 20–30% lower compared to a deceased donor kidney transplant recipients during 10- and 20-year follow-up, and 20% lower compared a living donor kidney transplant recipients during 20-year follow-up [16].

Pancreatic islet transplantation is a minimally invasive alternative to solid-organ pancreas transplantation and constitutes a safe surgical treatment method associated with no significant burden for the patient. This procedure is much easier and associated with a lower risk of complications but also with a much lower likelihood of achieving insulin independence. Transplantation outcomes depend mostly on the quality and quantity of infused islets per kg of body mass. Studies indicate that the desired amount that allows for a functional effect is at least 5000 islet equivalents (IEQ) per kilogram of body mass. Of an average of a million of islets that are present in the pancreas, it is usually possible to retrieve about 300–500 thousand IEQ.

Table 5. Igls classification for the evaluation of transplanted pancreatic islet function

Islet function	HbA_{1c} (%)	Severe hypoglycaemia episodes	Insulin requirement (U/kg/d)	Peptide C	Success
Optimal	≤ 6.5	Absent	No	> baseline value	Yes
Good	< 7.0	Absent	< 50% of baseline value***	> baseline value	Yes
Marginal	≥ 7.0	< baseline freqency*	≥ 50% of baseline value	> baseline value	No*****
Failed	As at baseline	As at baseline**	As at baseline	As at baseline****	No

HbA_{1c} — haemoglobin A_{1c}
*If severe hypoglycaemia episodes were present before islet transplantation, determining benefits from transplantation requires assessment of the occurrence of severe hypoglycaemia episodes (< 3 mmol/L or 54 mg/dL), hypoglycaemia unawareness, and variation/lability of blood glucose levels
**If severe hypoglycaemia episodes were absent before islet transplantation, baseline indications for treatment are reevaluated
***Also glucose-lowering drugs other than insulin
****It is not a reliable indicator in patients with advanced renal failure and detectable peptide C level before islet transplantation
*****Clinically, benefits may still outweigh the risk associated with maintenance and monitoring of the residual function of transplanted islets

Of the isolated islets, ultimately less than half survive and produce insulin. The ultimate effect of transplantation may only be assessed several weeks after the procedure, as the islets require some time to engraft i.e. restore appropriate vascular supply. Only then they are able to provide normal synthesis of insulin, glucagon and other peptides in response to nutritional stimuli and blood glucose level. Of note, the patients ultimately receive less than half of the normal amount of islets in a healthy person during a single pancreatic islet transplantation. Thus, even if insulin independence is achieved, these patients have borderline beta cell function and only a small metabolic reserve. Reinitiation of insulin may be necessary with increased carbohydrate/caloric intake, reduced exercise, or weight gain. Reduced insulin sensitivity is compensated by its increased secretion by beta cells. It seems that similarly to increased insulin resistance in diabetes type 2, compensatory hyperinsulinemia leads to exhaustion of the secretory function of the transplanted beta cells. Two or three sequential pancreatic islet transplantation procedures are usually necessary. According to the 2016 CITR data, insulin independence at 5 years was achieved in only 30% of patients after pancreatic islet transplantation alone and in 20% of patients after pancreatic islet transplantation following earlier kidney transplantation. Reports from single centres vary, with the proportion of patients showing insulin independence at 5 years ranging from 10% to as much as 60%. According to the most recent reports from France, although more than 60% of patients achieved insulin independence, the effect persisted at 5 years in less than 20% of patients [17, 18].

Achieving insulin independence, although possible, particularly with repeated islet infusions from several donors, is not the major goal of pancreatic islet transplantation. The main goals are to stabilize the disease course, minimize the risk of chronic complications, and significantly reduce or even eliminate the risk of life-threatening severe hypoglycaemia. This has been reflected in the Igls classification designed to evaluate the function of transplanted pancreatic islets, developed in January 2017 based on the expert consensus during the 1st IPITA/EPITA Opinion Leaders Workshop in Igls, Austria (Table 5). Restoration of endogenous insulin secretion following pancreatic islet transplantation has a beneficial effect on lipid abnormalities, and preserved peptide C secretion, even in the absence of insulin independence, markedly limits the development of secondary diabetes complications, reducing the rate of life-threatening hypoglycaemia and protecting from the development of diabetic nephropathy, retinopathy, and enteropathy [19]. Even with only residual graft secretory function, patients do not experience severe symptomatic hypoglycaemia [20].

It seems that both approaches, i.e., solid-organ pancreas transplantation and isolated pancreatic islet transplantation may be considered complementary methods. In case of failed solid-organ pancreas transplantation, pancreatic islet transplantation may be offered and vice versa. Both solid-organ pancreas transplantation and pancreatic islet transplantation were shown to be beneficial in terms of reduced progression of macro- and microvascular complications compared to the conventional treatment [4–10].

The similarities of and differences between solid-organ pancreas transplantation and pancreatic islet transplantation are summarized in Table 6.

Total pancreas resection with pancreatic islet autotransplantation

It should be noted that pancreatic islet autotransplantation is performed in patients undergoing total pancreatectomy due to intractable pain related to chronic pancreatitis. This procedure allows removal of the fibrosed pancreas and infusion of the isolated islets, even if not always providing insulin independence,

Table 6. Comparison of solid-organ pancreas transplantation and pancreatic islet transplantation

Pancreatic islet transplantation	Solid-organ pancreas transplantation
Minimally invasive procedure involving percutaneous transhepatic puncture of a portal vein branch, usually under local anaesthesia	Major intrabdominal surgery requiring general anaesthesia
Complication rate about 10%, mostly bleedings and hematomas not requiring transfusion	Complication rate about 30%, including 1/3 leading to a loss of the transplanted organ. Complications often require reoperation
Usually 2–3 sequential transplantations are needed	Single procedure
Need for immunosuppressive therapy	Need for immunosuppressive therapy
Reduces the risk of severe hypoglycaemia	Reduces the risk of severe hypoglycaemia
Low likelihood of achieving durable non-insulin dependence	High likelihood of achieving durable non-insulin dependence

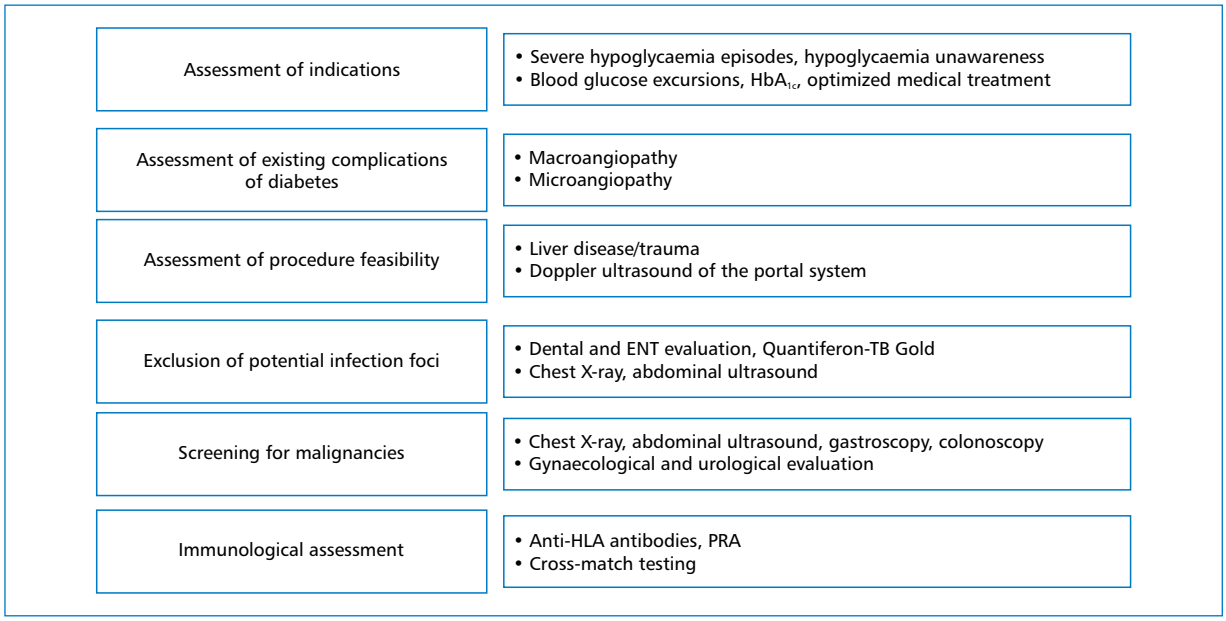

Figure 2. Patient selection for pancreatic islet transplantation. ENT — ear, nose, and throat; HbA_{1c} — haemoglobin A_{1c}; HLA — human leukocyte antigen; PRA — panel reactive antibodies

protects from excessive blood glucose level excursion and severe hypoglycaemia episodes. Selected centres worldwide have attempted pancreatic islet autotransplantation in patients undergoing total pancreatectomy due to both benign and malignant tumours [21, 22].

Referral of a patient with brittle diabetes type 1 for pancreas or pancreatic islet transplantation

The approach to patient selection for pancreatic islet transplantation is shown in Figure 2. Patient selection for solid-organ pancreas transplantation is generally similar. A patient who fulfils the selection criteria and does not fulfil the disqualification criteria, based on the assessment of the general status, cardiovascular fitness, and technical feasibility of the procedure, after excluding infections and malignancies, is placed on the National Waiting List. The formal patient registration and selection occurs via the Transplantation Registry of the Ministry of Health (https://rejestrytx.gov.pl/tx/). The patient is registered by a physician from the pancreatic islet/pancreas transplantation centre. The recipient receives pancreatic islets from a donor with a compatible main blood group. Within the waiting list, priority is assigned to patients with the same main blood group and the lowest number of incompatible HLA antigens. Immediately before transplantation, cross-match testing is performed using the serologic technique. Lymphocytes for cross-match testing are obtained from the lymph nodes of a deceased donor and exposed to the sera of potential recipients on the waiting list. Only the recipients with a negative cross-match test, i.e., without

cytotoxic antibodies against donor HLA antigens, may be then considered for transplantation. Transplantation is then performed only if pancreatic islets of appropriate quantity and quality are isolated. Similarly to patients awaiting kidney transplantation from a deceased donor, the complement-dependent cytotoxicity test with panel reactive antibodies (PRA-CDC) and anti-HLA antibody solid phase assays are periodically performed to assess the degree of immunization.

Summary

Currently, both solid-organ pancreas transplantation and pancreatic islet transplantation remain the only methods that allow restoration of physiologic endogenous insulin secretion. Pancreatic islet transplantation is a minimally invasive alternative to solid-organ pancreas transplantation and constitutes a safe surgical treatment method associated with no significant burden for the patient. It seems the optimal approach particularly in a kidney or another solid-organ transplant recipients who already receive immunosuppressive therapy to prevent rejection of the other transplanted organ.

Despite advances in the islet isolation technique and immunosuppressive therapy, a progressive loss of function of the transplanted islets is observed, and in most cases insulin independence is limited in time even in case of good baseline function of the transplanted beta cells. Thus, achieving insulin independence, is not the major goal of pancreatic islet transplantation. The main goals are to stabilize the disease course, minimize the risk of secondary complications, and eliminate the risk of life-threatening severe hypoglycaemia episodes. Solid-organ pancreas transplantation is associated with a higher risk of complications but offers a much higher likelihood of achieving insulin independence. Both these approaches to beta cell replacement seem a valuable therapeutic option in patients with brittle diabetes type 1, hypoglycaemia unawareness and recurrent severe hypoglycaemia episodes despite appropriate education and optimized medical management.

Conflict of interest

The authors report no conflicts of interest.

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