ISLET TRANSPLANTATION

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Updated September 9, 2022

ABSTRACT

Transplanting islets of Langerhans consists of implantation in the recipient's hepatic portal system of endocrine pancreatic tissue, with a variable degree of purification. The field of islet transplantation has evolved significantly since the initial attempts by doctors *Minkowski* and *von Mering* in 1882, with remarkable acceleration over the last four decades, thanks to the incredible efforts of the research community worldwide, with continuous improvements in cell processing and transplantation techniques, patient management and development of specific immunotherapy protocols. Restoration of beta-cell function can be obtained by transplantation of allogeneic islets in both non-uremic (Islet Transplant Alone, ITA) and uremic (Simultaneous Islet and Kidney, SIK and Islet After Kidney, IAK) patients with diabetes, providing long-term sustained function and improved metabolic control even when requiring exogenous insulin (*i.e.*, suboptimal islet mass transplanted or development of graft dysfunction). Preservation of beta-cell function is now attained in virtually all recipients of islet autografts, a therapeutic option that should be considered for individuals undergoing total pancreatectomy for non-malignant conditions and, as recently reported for selected cases with malignant conditions. In addition, islet transplantation represents an excellent platform toward the development of cellular therapies aimed at the restoration of beta-cell function using stem cells in the near future. In this chapter, we will review the state-of-the art of clinical islet transplantation.

INTRODUCTION

Diabetes affects 537 million adults (20-79 years) throughout the world (2021) and this number will rise to 643 million by 2030 and 783 million by 2045 (**IDF Diabetes Atlas 10th edition**, https://diabetesatlas.org/). Many cases of diabetes are successfully treated with life-long multiple daily injections of exogenous insulin and monitoring of blood glucose levels. In the last decades significant improvements in insulin therapy thanks to new preparations (i.e., ultrafast and long-lasting insulin analogues) and the adoption of intensive diabetes management (infusion pumps and continuous glucose monitoring system) have resulted in an overall improvement of patients' glycemic control and a decreased incidence of chronic complications of diabetes (1,2). However, exogenous insulin administration cannot attain the desirable tight control in the majority of diabetics (3-5), cannot avoid the long-term complications of diabetes in all patients and the life expectancy of patients with diabetes is still shorter compared to that of the general population (6-8). A broad international assessment of treatment outcomes in children and adults with T1D (including 324,501 people from 19 countries in Australasia, Europe and North America) showed that

the proportion of patients with HbA1c <7.5% (58 mmol/mol) varied from 15.7% to 46.4% among 44,058 people aged < 15 years, from 8.9% to 49.5% among 50,766 people aged 15-24 years and from 20.5% to 53.6% among 229 677 people aged ≥ 25 years (9). Diabetes is one of the leading causes of end-stage renal disease, blindness and amputation (10). In principle, the treatment for type 1 diabetes, type 3c diabetes and many cases of type 2 diabetes lies in the possibility of replacing destroyed or exhausted beta cell mass in order to restore two essential functions: sensing blood sugar levels and secreting appropriate amounts of insulin in the vascular bed, ideally into the portal system. Currently, the only available clinical approach of restoring beta cell mass in patients with diabetes is the allogenic/autologous transplantation of beta cells (i.e., pancreas or islet transplantation). Clinical trials performed in the last three decades have shown that restoration of beta-cell function *via* transplantation of isolated islet cells or vascularized pancreas allows reproducibly achievement of a more physiological release of endocrine hormones than exogenous insulin in subjects with diabetes (11). Transplanting islets of Langerhans consists of implantation in the recipient's hepatic portal system of endocrine pancreatic tissue, with a variable degree of purification. Isolated islets are transplanted using minimally invasive techniques with lower morbidity than vascularized pancreas transplantation, which requires major surgery. The field of islet transplantation has evolved significantly since the initial attempts by doctors *Minkowski* and *von Mering* in 1882 (12), with remarkable acceleration over the last three decades, thanks to the incredible efforts of the research community worldwide, with continuous improvements in cell processing and transplantation techniques, patient management and development of specific immunotherapy protocols. In addition, islet transplantation represents an excellent platform toward the development of cellular therapies aimed at the restoration of beta-cell function using stem cells in the near future. In this chapter, we will review the state-of-the art of clinical islet transplantation.

WHEN TO CONSIDER ISLET TRANSPLANTATION?

Transplantation of pancreatic islet may be considered as a therapeutic option in several conditions associated with loss of beta-cell function (Table 1). The procedure may be performed as **Islet Transplant Alone** (**ITA**) in non-uremic subjects, an option generally indicated for the treatment of iatrogenic (surgery-induced) diabetes and for non-uremic patients with Type 1 Diabetes. Subjects with end-stage renal disease (ESRD) may be considered for **Simultaneous Islet-Kidney** (**SIK**) or, if already undergone renal transplantation, **Islet After Kidney** (**IAK**) transplantation, respectively. In special situations, transplantation of islets may be considered in combination with other organs (*i.e.*, in the context of multi-visceral transplantation following exenteration comprising the pancreas) (13).

The source of the islets for transplantation may be the patient's own pancreas (**autologous** or **auto-transplant**) mainly when surgical removal of the gland is required due to different conditions. After total pancreatectomy, the subject develops **surgery-induced (iatrogenic) insulin-requiring diabetes**. Introduced in the early 1970's (14), islet auto-transplantation allows achieving optimal metabolic control without the need for exogenous insulin in approximately 70% of the cases when adequate islet numbers can be recovered from the pancreas (generally >250,000 islet equivalents). More than 500 **auto-transplant** in patients with near-total or total pancreatectomy have been performed to date (15). The largest series were published by the University of Minnesota (16-19), the University of Cincinnati (20,21), and Leicester (22-25). Even when an inadequate islet mass to attain insulin-independence has been recovered, stable metabolic control and excellent management can be achieved in most subjects undergoing autologous islet transplantation (18,26-31). Islet auto-transplantation

is currently reimbursed by health insurance in the United States. In the past **auto-transplant** has been performed almost exclusively in patients undergoing pancreatectomy because of chronic pancreatitis, successfully preserving β-cell mass and preventing diabetes after major pancreatic resections (15,16,32,33). Additional indications for **auto-transplant** other than chronic pancreatitis are still controversial (34), and have been limited to the procedure performed only in small case series (35-40) of benign enucleable tumors or pancreatic trauma. Recently, broader selection criteria for **auto-transplant** were published (39,41), exploring the possibility of extending **auto-transplant** to patients with known malignancy, either having completion pancreatectomy as treatment for severe pancreatic fistulae or extensive distal pancreatectomy for neoplasms of the pancreatic neck or pancreatoduodenectomy because at high risk of pancreatic fistula (Table 1). Of note, a randomized, open-label, controlled, bicentric trial (NCT01346098) aimed to compare pancreaticoduodenectomy (PD) and Total Pancreatectomy with Islet AutoTransplantation (TP-IAT) in patients at high risk of Post-Operative Pancreatic Fistula (POPF) was recently published. The results indicate that TP-IAT can be considered a valid alternative to PD in these patients, as it reduced complication number, severity and length of hospital stay. Of note, a trend toward a reduction of mortality, even for patients with malignancy was also evident. As expected, TPIAT was associated to a higher risk of diabetes, but IAT was able to preserve, at least in part, the endogenous insulin secretion, mitigating the impact of the pancreoprivic diabetes and assuring a good metabolic control without severe hypoglycemic episodes. In the field of islet transplantation, this study definitively confirmed IAT could be indicated for pancreas diseases other than chronic pancreatitis, suggesting the possibility to extend IAT indications (Milan protocol(42)). For the first time in a randomized prospective design, it was confirmed that IAT is feasible, safe and effective in patients with periampullary cancer, in agreement with previous series of patients undergoing IAT after pancreatic resection for a wide spectrum of disease besides chronic pancreatitis (43) (44) (37). This approach will be tested in further studies in the next years, such as the recently started TPIAT-01 trial (NCT05116072), which hypothesize that TPIAT rather than PD may improve the access to adjuvant chemotherapy in patients with adenocarcinoma.

In the case of subjects who lost islet function (mainly patients with Type 1 Diabetes or, more rarely, previous total pancreatectomy) the only option currently available for transplantable islet cells is **allogeneic** donor pancreata. These are generally obtained through multi-organ donation after cerebral death, following conventional donor:recipient ABO blood type matching. The use of a segment of the pancreas from living-related donors is technically feasible (45,46), but at the present time not preferred for islet transplantation due to the limited duration of graft function after transplantation of suboptimal islet numbers under standard immunosuppressive protocols, as well as the intrinsic risks for the donor (*i.e.*, morbidity and risk to develop diabetes)(47).

Table 1. Indication for Islet Transplantation

Condition	**Procedure**	**Type of Transplant**
Diabetes Mellitus		
Type 1	ITA, SIK, IAK	Allogeneic
Type 2	ITA, SIK, IAK	Allogeneic

Surgery-Induced Diabetes (Iatrogenic)		
Chronic pancreatitis	ITA	Autologous/Allogeneic
Trauma	ITA	Autologous/Allogeneic
Multi-visceral transplantation	Different combinations: Liver-Islet Transplantation, Bowel-Liver-Islet Transplantation, etc.	Allogeneic
Cystic Fibrosis	ITA Lung-Islet Transplantation	Autologous/Allogeneic Allogeneic
Benign enucleable tumors	ITA	Autologous
Borderline/malignant pancreatic neoplasms	ITA	Autologous/Allogeneic
Grade C pancreatic fistula requiring completion pancreatectomy	ITA	Autologous/Allogeneic

ITA- Islet Transplant Alone; SIK- Simultaneous Islet-Kidney; IAK- Islet After Kidney

The current main indication for an allogeneic islet transplant is **Type 1 Diabetes**, which is characterized by the selective destruction of islet beta cells due to an autoimmune process. Ongoing clinical trials of allogeneic islet transplantation are recruiting subjects with unstable Type 1 Diabetes 18-65 years of age, either sex, with frequent metabolic instability requiring medical treatment (hypo-, hyper-glycemia, ketoacidosis) despite intensive insulin therapy; hypoglycemia unawareness (<54mg/dL); severe metabolic lability (mean amplitude of glycemic excursion >11,1 mmol/L or 200 mg/dl). The inadequate efficacy of medical therapy to attain the desirable metabolic control in this specific patient population with unstable diabetes justifies the use of transplantation of pancreatic islets (either isolated cellular graft or vascularized whole pancreas) (48). **The main objective of the transplant is to correct the high susceptibility to severe hypoglycemia and glycemic imbalance** that are associated with high mortality (8% in nonuremic subjects in the waiting list for 4 years to receive pancreas transplantation). Further indications for an islet transplant are presence of progressive complications of diabetes and psychological problems with insulin therapy that may compromise adherence to the therapeutic regimen. Islet transplant is indicated also for cases of subcutaneous insulin resistance requiring intraperitoneal or intravenous infusions, which are associated with substantial management hurdles and morbidity.

Table 2. Inclusion and Exclusion Criteria for Allogeneic Islet Transplantation in T1DM*

Inclusion Criteria:

- Mentally stable and able to comply with study procedures
- Clinical history compatible with type 1 diabetes with onset of disease at <40 years of age, insulin dependence for at least 5 years at study entry, and a sum of age and insulin dependent diabetes duration of at least 28
- Absent stimulated C-peptide (<0.3 ng/ml) 60 and 90 minutes post-mixed-meal tolerance test
- Involvement of intensive diabetes management, defined as:
  - Self-monitoring of glucose values no less than a mean of three times each day averaged over each week
  - Administration of three or more insulin injections each day or insulin pump therapy
  - Under the direction of an endocrinologist, diabetologist, or diabetes specialist with at least three clinical evaluations during the past 12 months prior to study enrollment
- At least one episode of severe hypoglycemia in the past 12 months, defined as an event with one of the following symptoms: memory loss; confusion; uncontrollable behavior; irrational behavior; unusual difficulty in awakening; suspected seizure; seizure; loss of consciousness; or visual symptoms, compatible with hypoglycemia in which the individual required assistance of another subject was unable to treat him/herself person and which was associated with either a blood glucose level <54 mg/dl or prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration in the 12 months prior to study enrollment
- Reduced awareness of hypoglycemia

Exclusion Criteria:

- Body mass index (BMI) >30 kg/m^2 or weight ≤50 kg
- Insulin requirement of >1.0 IU/kg/day or <15 U/day
- HbA1c >10%
- Untreated proliferative diabetic retinopathy
- Systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg
- Measured glomerular filtration rate using iohexol of <80 ml/min/1.73mm^2.
- Presence or history of macroalbuminuria (>300 mg/g creatinine)
- Presence or history of panel-reactive anti-HLA antibody levels greater than background by flow cytometry.
- Pregnant, breastfeeding, or unwilling to use effective contraception throughout the study and 4 months after study completion
- Presence or history of active infection, including hepatitis B, hepatitis C, HIV, or tuberculosis.
- Negative for Epstein-Barr virus by IgG determination
- Invasive aspergillus, histoplasmosis, or coccidioidomycosis infection in the past year
- History of malignancy except for completely resected squamous or basal cell carcinoma of the skin

- Known active alcohol or substance abuse
- Baseline Hgb below the lower limits of normal, lymphopenia, neutropenia, or thrombocytopenia
- History of Factor V deficiency
- Any coagulopathy or medical condition requiring long-term anticoagulant therapy after transplantation or individuals with an INR greater than 1.5
- Severe coexisting cardiac disease, characterized by any one of the following conditions:
  - Heart attack within the last 6 months
  - Evidence of ischemia on functional heart exam within the year prior to study entry
  - Left ventricular ejection fraction <30%
- Persistent elevation of liver function tests at the time of study entry
- Symptomatic cholecystolithiasis
- Acute or chronic pancreatitis
- Symptomatic peptic ulcer disease
- Severe unremitting diarrhea, vomiting, or other gastrointestinal disorders that could interfere with the ability to absorb oral medications
- Hyperlipidemia despite medical therapy, defined as fasting LDL cholesterol >130 mg/dl (treated or untreated) and/or fasting triglycerides >200 mg/dl
- Currently receiving treatment for a medical condition that requires chronic use of systemic steroids except for the use of 5 mg or less of prednisone daily, or an equivalent dose of hydrocortisone, for physiological replacement only
- Treatment with any antidiabetic medication other than insulin within the past 4 weeks
- Use of any study medications within the past 4 weeks
- Received a live attenuated vaccine(s) within the past 2 months
- Any medical condition that, in the opinion of the investigator, might interfere with safe participation in the trial
  - Treatment with any immunosuppressive regimen at the time of enrollment.
  - A previous islet transplant.
- A previous pancreas transplant, unless the graft failed within the first week due to thrombosis, followed by pancreatectomy and the transplant occurred more than 6 months prior to enrollment.

*Modified from the information relative to active trials from the Clinical Islet Transplant Consortium (www.citisletstudy.org/) as listed at http://clinicaltrials.gov/ct2/show/NCT00434811.

MULTIDISCIPLINARY TEAM

Islet Transplant Programs require the integration of multidisciplinary expertise. The endocrinologist expert in diabetes diagnosis and management is

essential member of the team, and can identifying subjects who may benefit of beta-cell replacement therapy, and help with the evaluation of metabolic control during all phases of the follow-up. The psychologist is involved in the evaluation of islet transplant candidates to assess their motivation, mental fit to enroll in the trial, and ability to adhere to the therapy. Psychometric and psychological evaluations are performed during the follow-up period after transplantation. Transplant surgeons provide the expertise in organ procurement, with transplant procedures, overall management of patients and immunosuppression. A dedicated Cell Transplant Center with specialized experts in pancreatic cell isolation, purification, culture, potency assessment and quality assurance warrant that islet cell products are manufactured for clinical transplantation following cGMP standards and FDA regulations. The interventional radiologist performs the noninvasive cannulation of the portal vein and participates to the post-transplant monitoring of the liver using noninvasive imagine techniques. The organ procurement organizations and organ distribution networks (UNOS in the U.S.) contribute to the identification and allocation of donor organs matching the recipient's characteristics. The ophthalmologist and nephrologist are involved to monitor and treat progressive diabetic complications (i.e., retinopathy and renal function, respectively).

ISLET ISOLATION AND TRANSPLANTATION

Islets are highly vascularized cell clusters ranging <50um to ~800um of diameter that constitute the endocrine component of the pancreas. It has been estimated that a healthy pancreas may contain approximately 10^6 islets scattered throughout the gland, and accounting for only ~1% of total pancreatic tissue. Each cluster comprises several thousands of endocrine cell subsets that are closely in touch with capillaries and with each other. Complex cell-cell interactions between different cell subsets, innervation, incretins and metabolites (sugar and amino acids, amongst other) in the blood and interstitial space all contribute to the proper control of glucose homeostasis (49). Preservation of the integrity of islet cell cluster is a prerequisite for their optimal function. The procedure currently used to extract islets from human pancreas is the so called automated method for isolation of the islets of Langerhans, established in 1987 by Ricordi and colleagues (50). Before the beginning of the isolation procedure, the spleen and the duodenum are removed from the pancreas and an accurate dissection and removal of the peripancretic fat, lymph nodes and vessels is performed. Then, the pancreas is divided at the neck and two 16-20 gauge angiocatheters are inserted into the main pancreatic ducts. The organ is then perfused with cooled perfusion solution containing collagenase and serine – protease inhibitor – dissolved in buffer at a pressure of 140-180 mmHg. After 10 minutes of cold perfusion, the distended pancreas is further cut into smaller sections, and placed into the Ricordi chamber. This chamber is composed of a superior and an inferior part, separated by a filter that has pores of about 700μm. Seven to nine stainless steel balls and the fragments of the pancreas are placed into the inferior part of the chamber, which is then filled with the digestion solution and closed together with the superior part of the chamber. A peristaltic pump connected to the system is activated creating a flow of 40 ml/min. The digestion runs in a closed circuit where warm Hank's solution is pumped in the inferior chamber and the tissue released in the solution passes in the superior chamber through the filter. The collagenase is re-circulated at a temperature not exceeding 37°C and the chamber is agitated. When most of the islets are free of the surrounding acinar tissue, and intact islets are observed, the heating circuit is bypassed. The temperature is progressively decreased to 10°C and the collagenase diluted with cold RPMI. The free islets are then collected in containers, washed several times, re-suspended in cold organ preservation solution and purified with a continuous ficoll gradient using a Cobe 2991 cell separator. At the end of the procedure samples of the islet

preparation are collected and evaluated through staining with dithizone (DTZ) which marks zinc in the insulin granules, resulting in a characteristic red stain. Adding few drops of DTZ solution to a sample allows easy evaluation of the morphology and number of isolated islets through computerized digital analysis. The islet manufacturing processes must be controlled by different assays and the islet batch product validated and characterized. Then safety testing is carried out for sterility and pyrogenicity, identity (insulin content), cell number (amount of tissue, counting of islets), purity (percentage of ductal, acinar, beta, and other cells), viability (islet nucleotide content), potency (insulin secretory response) and finally stability (storage in culture). Specific features of the final islet preparation are a required for islet preparations used in islet transplantation, in particular purity (> 20% of the preparation being islets), adequate number of islets (>5,000 islet equivalent recipient body weight for the first infusion, >3,000 for further infusions) and total tissue volume (< 5 ml). The infusion of the islets can be performed a few hours after the end of the isolation process or up to 72 hours thereafter. The implantation site is usually the hepatic parenchyma through the portal system of the recipient. Recently other implantation sites have been proposed (51) in the clinical setting, like the bone marrow (52,53), the subcutaneous site(54), the gastric submucosa (55), the omentum(56,57) or striated muscle (58,59), which in the future, may prove to be valid alternative sites for islet transplantation. The adequate amount of islets obtained is calculated with respect to the body weight of the recipient and re-suspended immediately before intrahepatic transplantation in 40-60 mL of a solution suitable for injection (Ringer Lactate, 1% Human Albumin and 2000 IE of heparin). Percutaneous trans hepatic catheterization is the most common access route, as well as a mini-laparotomy and cannulation of an omental or mesenteric vein, or recanalization of the umbilical vein. Access to the portal vein is usually provided by interventional radiologists. If the portal pressure is documented to be below 20 mmHg, the islet infusion bag is connected with the portal vein catheter and infused over a period of 15 to 60 minutes. Islet infusion is halted if the portal pressure exceeds 22 mmHg. After completion of the islet infusion, the catheter is withdrawn; coils and gelatin-sponges are deployed in the puncture tract to prevent bleeding. A schematic animation of the islet isolation and transplant procedures is available online [http://www.youtube.com/watch?v=aMNKu-ZVUIs].

THE CONSORTIUM CONCEPT

A major development in the field of islet transplantation is the combination of individual centers into larger groups such as the GRAGIL network in France and Switzerland, the Nordic Network for Clinical Islet Transplantation (NNCIT) in the Scandinavian countries and the Clinical Islet Transplant Consortium (CITC) internationally but concentrated in North America. The need for dedicated infrastructures and personnel specialized in islet cell processing, quality assessment and cGMP standards impose an enormous financial burden on any Clinical Islet Transplant Program. Acquiring and maintaining the specialized expertise in islet cell processing requires a steep learning curve and continuous refinements and training that add to the costly procedure. Recent data have shown that the experience of the clinical islet transplant team in cell processing and management of immunosuppression are critically important in determining the success of a clinical trial (60). Based on these premises, the development of regional cell processing centers that are part of consortia that are integrated with distant transplant centers is increasingly being considered as a practical and cost-effective strategy (Figure 1). Initial reports of successful clinical trials carried on in the context of Consortia both in Europe and North America (61-64) support the feasibility of such an approach, which may be of assistance in reducing the operational costs while enhancing the success rate of clinical trials (*i.e.*, better utilization of donor pancreata, more

reproducible success in obtaining adequate numbers of functional islets from a donor pancreata, etc.).

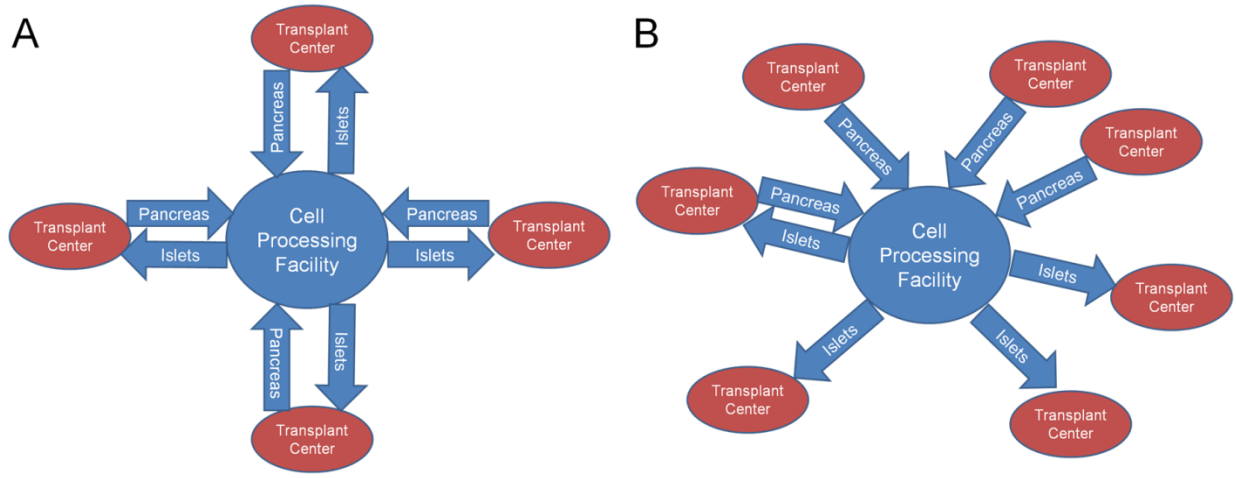

Figure 1. Islet Transplant Consortium Models. A. The centralized (or 'regional') Cell Processing Facility receives the donor pancreas from a distant Transplant Center and isolates islet cell products that are sent back for implant. B. The centralized Cell Processing facility receives the donor pancreas from one of the Transplant Centers and distributes the isolated islets to any of the Transplant Center in the Consortium according to the best match of the cell product for the transplant candidate on the waiting list for transplant (that is, the islet cell product is not necessary returned to the center recovering the pancreas).

ISLET TRANSPLANT ACTIVITY

The Collaborative Islet Transplant Registry (CITR)

In 2001, the National Institute of Diabetes & Digestive & Kidney Diseases established the Collaborative Islet Transplant Registry (CITR) to compile data from all islet transplant programs in North America from 1999 to the present. The Juvenile Diabetes Research Foundation (JDRF) granted additional funding to include the participation of JDRF-funded European and Australian centers from 2006 through 2015. The cumulated North American, European and Australian data are pooled for analyses included in the annual report. CITR Annual Reports are publicly available as open access and can be downloaded or requested in hard copy at www.citregistry.org. From 1999 through 2020 – the cut-off for the last Eleventh Annual Report – CITR has collected data on the following groups of study subjects:

a) Allogeneic islet transplantation (typically cadaveric donor), performed as either islet transplant alone (ITA) or islet-after-kidney (IAK). A small number of cases have been performed as islet simultaneous with kidney (SIK) or kidney-after-islet (KAI).
b) Autologous islet transplantation, performed after total pancreatectomy (N=1,233) are also reported to CITR.

As of December 15, 2020, the CITR Registry included data on 1,399 allogeneic islet transplant recipients (1,108 islet transplant alone, ITA, and 236 islet after kidney, IAK, 49 simultaneous islet kidney, SIK, and 6 kidney after islet, KAI), who received 2,832 infusions from 3,326 donors. From 1999 through 2020, 28 National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) sponsored North American and 12 international Eurasian and Australian islet transplant centers (40 total) contributed data to the Collaborative Islet Transplant Registry (CITR). Combining the ITA and IAK

recipients, 27.4% received a single islet infusion, 48.1% received two, 20.4% received three, and 4.1% received 4-6 infusions. Of 26 North American sites performing Auto-ITx from 1999 through December 2020, 15 reported data to CITR along with 5 European and Australian islet transplant centers. These sites registered 1233 autoislet transplant recipients. Of these, 1123 recipients were in North America, 98 in Europe, and
12 in Australia. One-hundred eight-five (185) were aged less than 18, and 1,057 were 18 or older at the time of their transplant.

Outside The Collaborative Islet Transplant Registry (CITR)

Although the CITR is an extraordinary source of valuable data, a recent publication indicates that it does not capture a major part of the international islet transplant activities and outcomes (65). In fact, a global online survey was recently administered to 69 islet transplantation programs. After integration of all data obtained, 103 islet transplant centers were identified, of which 94, in 25 countries, had reported allotransplantation activity during the 2000–2020 period: 15 in Asia (16%), 39 in Europe (42%), 34 North America (36%), 3 in Oceania (3%) and 3 in South America (3%) and between January 2000 and December 2020, 4,321 islet allotransplants in 2,149 patients were reported worldwide. Most islet transplants were performed in Europe (2,608, 59.7%), followed by North America (1,475, 33.8%), Asia (135, 3.1%), Oceania (119, 2.7%) and South America (28, 0.6%). Actually the ANZIPTR (Australia and New Zealand Islet and Pancreas Transplant Registry) and NHS-BT (UK National Health Service-Blood and Transplant) registry are publicly available registries containing a wealth of data on islet and pancreas transplantation in Australia/New Zealand and UK, respectively, including outcomes (66) (67). The European Pancreas and Islet Transplant Registry (EPITR) is a current effort from ESOT/EPITA aiming at covering these needs for Europe (https://esot.org/epita/epita-epitr/).

CLINICAL MANAGEMENT OF ISLET TRANSPLANT RECIPIENTS

The clinical management of islet transplant recipients requires the concerted effort of endocrinologist and transplant teams.

Immunosuppression

Preexisting and transplant-induced auto- and allo-specific cellular immune responses play a crucial role in the loss of islets and islet function infused in the liver (68-70) along with non-specific immune responses predominantly mediated by innate inflammatory processes related to mechanics and site (71-74). Islet graft rejection occurs without clinical symptoms. Neither guidelines nor formal consensus on the “best” or “standard” immunosuppressive strategy for human islet transplantation are currently available. Multiple induction and maintenance agents are administered peri- and post- every infusion in the same recipient. According to CITR data (75), a substantial shift in immunosuppression strategies has been documented during the last years.

Induction with interleukin-2 receptor antagonist (e.g., daclizumab) only, which comprised about 53% of all initial infusions in 1999-2002, was replaced or supplemented with regimens that included T-cell depletion with/without TNF antagonists in about 67% of the new infusions performed since 2015 (11,76-83). In 1999-2002, maintenance immunosuppression was predominantly (64%) calcineurin (CNI) +mTOR inhibitors (60). It was increasingly replaced or supplemented throughout the eras by a CNI and IMPDH-inhibitor combination (77,84-86).; in the most recent era, CNI+mTOR inhibitors were used in 15% of new infusions while CNI+IMPDH inhibitors were used in about 62%. Moreover, the use of

alemtuzumab-induction therapy was recently reported and associated with encouraging longer-term function (87,88). New biologic agents with potentially lower islet cell and organ toxicity profiles are currently being evaluated in ongoing clinical trials. Amongst these are agents that target co-stimulation pathways in immune cells and/or adhesion molecules (CTLA4-Ig, LFA-1 PD-1/PD-L1 CD40) (89-95) or chemokine receptors (CXCR1/2) (71,96). Finally, calcineurin inhibitor-free immunosuppressive regimen was reported (97).

Antibiotic and Antiviral Prophylaxis

Subjects receiving immunosuppression therapy are more susceptible to opportunistic infections, as well as reactivation or *de novo* occurrence of viral infections. Antibiotic prophylaxis for *Pneumocystis carinii* consists in trimethoprim and sulfamethoxazole three times a week. Antiviral prophylaxis is aimed are reducing the risk, or treating the occurrence, of cytomegalovirus infections (which have been recognized increasing the risk of graft loss in solid organ transplantation) and of reactivation of Epstein - Barr virus infection (which has been associated with the dreadful post-transplant lymphoproliferative disease, PTLD). Current protocols utilize antiviral therapy with vanglancyclovir daily for the first trimester post-transplant. Monitoring of viremia in peripheral blood samples by PCR is becoming a routine during the follow-up as it allowed for the early detection of reactivation or de novo infections that may be treatable without compromising graft outcome (98,99).

Thromboembolism Prophylaxis

It has been recognized that isolated islets produce tissue factor and other pro-inflammatory molecules that may trigger an instant blood-mediated inflammatory reaction upon infusion into the blood stream. This, in turn, may enhance the generation of noxious stimuli after embolization in hepatic sinusoids of the liver, significantly reducing the mass of functional islets engrafting. An aggressive heparin treatment is generally implemented in the early period after transplant. Heparin is added to the transplant medium used during the islet infusion, while low molecular weight heparin injections are administered in the post-transplant period. This is aimed at enhancing islet engraftment in the hepatic portal system while reducing the risk of portal thrombosis.

Peri-transplant Insulin Management

Islet engraftment may take up a few weeks to allow for neovascularization of the clusters in the transplant microenvironment. The monitoring of glycemic control in the immediate post-transplant period should be intense to attain tight glycemic values in order to avoid excessive workload for the newly transplanted islets as well as to prevent hypoglycemic episodes. This is generally done by providing basal exogenous insulin that is then progressively reduced and withdrawn according to the glycemic values measured.

POST-TRANSPLANT CLINICAL MONITORING

Monitoring of ***cell blood counts*** (erythrocytes, white blood cells and differential), hemoglobin, platelets and coagulation markers is routinely performed in the post-transplant period. These tests allow assessing the myelosuppressive effects of anti-rejection drugs. In the case of anemia with clinical relevance, iron supplementation may be indicated, while for more severe cases erythropoietin treatment is implemented. In the case of severe neutropenia, marrow stimulation with granulocyte-colony stimulating factor (G-CSF) is promptly implemented.

Renal function is monitored periodically in the follow-up of islet transplant recipients to assess the impact of restoring beta-cell function on the progression of diabetic nephropathy, and also to

identify and timely correct potential nephrotoxicity of anti-rejection drugs (i.e., CNI and mTOR inhibitors). Standard serological tests (serum creatinine, azotemia), urine tests (spot and 24-hr collections) are frequently performed during the follow-up and glomerular filtration rates (GFR) estimated using different algorithms (i.e., MDRD). The nephroprotective effect of ACE inhibitors and of antagonists of angiotensin-receptor (ARB) in subjects with diabetes has been recognized, and their use is particularly indicated in transplant recipients treated with immunosuppressive drugs known for their negative effects on renal function (100-104). Elevations of blood pressure from the range 130/80 mmHg are promptly treated pharmacologically.

Monitoring of ***lipid levels*** and prompt treatment of dyslipidemia are important in transplanted patients. Some of the anti-rejection drugs (i.e., mTOR inhibitors) are prone to induce dyslipidemia, which in turn may have toxic effects on beta-cells or contribute to creating an unfavorable environment (i.e., steatosis) in the liver (105). Prophylactic use of statins targeting LDL cholesterol levels <100mg/dL can be contemplated for islet transplant recipients.

Liver function is monitored in the post-transplant period. It is common to observe a transient and self-limited elevation of liver enzymes (transaminitis) because of the embolization of islets into the liver sinusoids (106,107). This is often associated with hyper-echoic pattern of the liver parenchyma at ultrasound evaluation in the early days post-transplant. This phenomenon resolves spontaneously without the need for medical treatment. Ultrasound evaluation of the liver and abdominal cavity in the days post-transplant also allows identifying timely possible procedural complication of the transplant, such as portal thrombosis, peritoneal hemorrhage and alterations of echogenicity of hepatic parenchyma (108).

The ***immune monitoring*** after islet transplantation does not differ much from that of any other organ transplant (109). Basal and serial evaluation of Panel Reactive Antibodies (PRA) is performed to determine possible allosensitization against Human Leukocyte Antigens (HLA) class I and II of the Histocompatibility complex of transplanted tissue. Generally, maintenance of an adequate immunosuppressive regimen can prevent the development of alloantibodies, thereby preventing their deleterious effects on graft survival and function (i.e., chronic rejection leading to graft loss) (110-112). Nonetheless, development of alloreactivity against donor or non-specific antigens may develop whenever reduction (i.e., during infections, toxicity and drug conversion, amongst other causes) or suspension (i.e., after complete graft loss) of immunosuppression is needed (112,113). The autoimmune process underlying Type 1 Diabetes is associated with the appearance of antibodies against self-antigens (autoantibodies; i.e., towards GAD, IA-1 and insulin). Serial titration of autoantibody levels during the follow-up period may enable detecting a reactivation of the autoimmune process, measured as conversion to positive values in previously negative subjects, or increase of antibody titers. These have been associated with a lower rate of insulin independence and shorter duration of graft function after islet transplantation (60,70). New assays for additional autoantibodies (i.e., ZnT8) and for autoreactive T cells are under evaluation to help enhancing the sensitivity of immune monitoring for early detection of recurrence of autoimmunity, which may enable implementation of timely immune interventions to rescue the transplanted cells (114-116).

MONITORING ISLET GRAFT FUNCTION

Several metabolic parameters allow monitoring the function of transplanted islets (Table 3). Since only subjects with Type 1 Diabetes who have undetectable stimulated c-peptide (<0.3 ng/dl) before

transplant are recruited for an islet transplant, monitoring of basal and stimulated c-peptide offers an excellent biomarker of graft function, even when exogenous insulin is required. There is no consensus on which approach is most suited to accurately assess functional islet mass. Algorithms and indices that combine multiple parameters have been developed and proposed to help simplifying and obtaining objective functional assessment of islet transplant recipients (117-126). The main goal is to identify early changes that indicate propensity to graft dysfunction (*i.e.*, functional impairment during an infection, drug-induced toxicity). Stimulation tests are performed before (at enrollment) and during the follow-up after transplant to evaluate the functional potency of the transplanted islets in response to different secretagogues (*i.e.*, glucose, arginine, or mixed meal test). Insulin therapy is generally implemented when random glycemic sampling demonstrates on three subsequent occasions within the same week fasting values >140 mg/dl (7.8 mmol/L) and postprandial values >180 mg/dl (10.0 mmol/L), or after recording two consecutive A1c values >6.5%.

Table 3. Monitoring of Islet Graft Function

Standard	Stimulation	Indices
Glycosylated Hb (A1c)	Mixed Meal	Hypo score
Fasting glycemia	Intravenous glucose	Liability index
Postprandial glycemia	Intravenous arginine	Beta score
MAGE*		Beta 2 score
CGMS*		Basal C-peptide/Glucose ratio
Basal C-peptide		HOMA-B*
Daily insulin requirement		HOMA-IR*
		TEF*

*Abbreviations. CGMS: *Continuous Glucose Monitoring System*. MAGE: *Mean Amplitude of Glucose Excursions*. HOMA-B: Homeostasis Model Assessment – functional beta cell mass. HOMA-IR: Homeostasis Model Assessment – Insulin-Resistance. TEF: Transplant Estimated Function

THE IGLS SCORE

The lack of standardized definition of graft functional and clinical outcomes remains a source of concern in β-cell replacement influencing its recognition as a valid clinical option from the endocrinology community. In order to address this issue, the International Pancreas & Islet Transplant Association (IPITA) joined with the European Pancreas & Islet Transplant Association (EPITA) for a two-day workshop on "Defining Outcomes for β-Cell Replacement Therapy in the Treatment of Diabetes" in January 2017 in Igls, Austria. The main objective was to develop consensus on the definition of

function and failure of current and future forms of β-cell replacement therapies. As result of the workshop, an IPITA/EPITA Statement was recently published (127,128). This Statement introduces some relevant innovations in the field including a new classification for the definition of clinically successful outcome. The functional status and clinical success of a β-cell graft should be defined separately using the same components of assessment: the HbA_{1c}, severe hypoglycemic events, insulin requirements, and C-peptide. Concordantly, a four-tiered system was proposed to classify the functional outcomes of β-cell replacement:

- *optimal β-cell graft function*: HbA_{1c} ≤6.5%, the absence of any severe hypoglycemia, the absence of any requirement for exogenous insulin or other anti-diabetic drugs, and documentation of an increase over pre-transplant measurement of C-peptide
- *good β-cell graft function:* defined by: HbA_{1c} <7.0%, the absence of any severe hypoglycemia, a reduction by more than 50% from baseline in insulin requirements or the use of non-insulin anti-diabetic drugs, and documentation of an increase over pre-transplant measurement of C-peptide.
- *marginal β-cell graft function:* no modification of HbA_{1c}, the reduction of severe hypoglycemia, a reduction by less than 50% from baseline in insulin requirements, and documentation of an increase over pre-transplant measurement of C-peptide.
    - *failure β-cell graft function:* absence of any evidence for a clinical impact (no modification of $HbA_{1c,}$ incidence of severe hypoglycemia and insulin requirement) and clinically insignificant levels of C-peptide.

Clinically successful outcomes includes both optimal and good functional outcomes, implying that the use of exogenous insulin or other anti-diabetic drugs is not synonymous with graft loss or failure. Neither a marginal β-cell graft nor a failed β-cell graft is considered a clinically successful. However, if documented impairment in hypoglycemia awareness, frequent occurrence or exposure to severe hypoglycemia, or marked glycemic variability/lability is convincingly improved, then it may be appropriate to consider that the β-cell graft is clinically impactful also in marginal function and the benefit of maintaining β-cell graft function may outweigh risks of maintaining immunosuppression. This implies that hypoglycemia awareness, serious hypoglycemia, and glycemic variability/lability must be evaluated at baseline for monitoring whether a marginally functioning graft is continuing to provide any clinical impact.

IPI TA/ EPITA Statement has the merit of having introduced a defined concept of clinical success based on easily measurable parameters over time and with a wide consensus of international experts Implementation of this new β-cell replacement outcome definition and its use in publication will be critical to improve the performance and to reliably compare the different β-cell replacement strategies (129).

July 2019, a symposium at the 17th IPITA World Congress was held to examine the Igls criteria after 2 years in clinical practice, including validation against continuous glucose monitoring (CGM)-derived glucose targets, and to propose future refinements that would allow for comparison of outcomes with artificial pancreas system approaches. A new Igls 2.0 form composite criteria was suggested (130), in which clinical outcome based on glucose regulation is separated from β-cell graft function, with the latter considered only for further qualification of β-cell replacement modalities (Table 4-5).

Table 4. Proposed Igls Criteria 2.0					
Treatment outcome	**Glycemic control**		**Hypoglycemia**		**Treatment success**
	HbA_{1c}, % (mmol/mol)[a]	**CGM, % time-in-range**	**Severe hypoglycemia, events per y**	**CGM, % time < 54 mg/dl (3.0 mmol/L)**	
Optimal	≤6.5 (48)	≥80	None	0	Yes
Good	<7.0 (53)	≥70	None	<1	Yes
Marginal	≤Baseline	>Baseline	<Baseline[b]	<Baseline	No[c]
Failure	~Baseline	~Baseline	~Baseline[d]	~Baseline	No

Baseline, pretransplant assessment (not applicable to total pancreatectomy with islet autotransplantation patients).

Abbreviations: CGM, continuous glucose monitoring; HbA1c, glycated hemoglobin.

a Mean glucose should be used to provide an estimate of the HbA1c, termed the glucose management indicator, in the setting of disordered red blood cell life span.

b 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.

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

d If severe hypoglycemia was not present before β-cell replacement therapy, then a return to baseline measures of glycemic control used as the indication for treatment (6, 7) may be consistent with β-cell graft failure.

Table 5. Proposed Igls Criteria 2.0		
β-cell graft function[e]	**C-peptide, ng/mL (nmol/L) [f]**	**Insulin use or noninsulin antihyperglycemic therapy**
Optimal	Any	None
Good	>0.5 (0.17) stimulated ≥0.2 (0.07) fasting	Any
Marginal	0.3-0.5 (0.10-0.17) stimulated 0.1-<0.2 (0.04-<0.07) fasting	Any
Failure	<0.3 (0.10) stimulated <0.1 (0.04) fasting	Any

[e] Categorization of β-cell graft function must first meet treatment outcome based on measures of glucose regulation.

[f] May not be reliable in uremic patients and/or in those patients with evidence of C-peptide production before β-cell replacement therapy.

IMPACT OF ISLET TRANSPLANTATION ON METABOLIC CONTROL (TABLE 6)

Four successful large-scale Phase 3 clinical trials in islet transplantation have been published recently: CIT-07 (multicenter, single-arm)(131), CIT06 (pivotal trial) (132), TRIMECO (multicenter, open-label, randomized) (133) and REP0211 (multicenter, Double blind, randomized) (134). All these studies demonstrate that human islets, when transplanted in patients with T1D with impaired awareness of hypoglycemia and severe hypoglycemic events, can safely and efficaciously maintain optimal glycemic control (135). The clinical experience confirms that the most remarkable effect of the islet transplant is the abrogation of severe hypoglycemia and the recovery of hypoglycemia awareness, which persists after development of graft dysfunction and even several months after graft failure (and loss of detectable c-peptide) (136,137). Following islet transplantation, the restoration of β cell responses to secretagogue stimulation is observed, with improved insulin secretion ('first phase') in response to intravenous glucose, as well as increased c-peptide secretion in response to oral glucose. Normalization of glycemic threshold triggering the release of counter-regulatory hormones can be demonstrated during hypoglycemic clamp studies, even if without reaching normalization of the magnitude of the vegetative response; furthermore, quasi-normal glucagon secretion in response to hypoglycemia can be observed (138-142). In addition to controlling hypoglycemia, insulin independence can be achieved when an adequate islet mass is transplanted (143). After islet transplantation, 5-year insulin independence may be as high as 50%. A quarter of patients may remain insulin independent, with HbA1c concentrations of less than or equal to 6·5%, for at least 10 years, with either islet transplantation alone or islet-after-kidney transplantation (144) (145). Moreover, the glucose control associated with excellent islet graft function closely matches glucose values measured in healthy adults: median glucose 103 mg/dl (95-112), glucose standard deviation around the mean value 14 (11-20), 0% time >180 mg/dl, 0% time <54 mg/dl, HbA1c 5.6 (5-5.8) (146). Additionally, a significant improvement of quality of life after islet transplant has been documented by using standardized psychometric instruments and interviews carried on by psychologists (147-155). Associated with the better glucose control and the evidence of islet function (c-peptide secretion), a positive impact on the microvascular complications of T1D has been described while is less evident on the macrovascular complications (156). More specifically, a stabilization/slower progression of retinopathy (104,157-159) and neuropathy (158,160-162) and an improvement of micro- and macroangiopathy (79,101,102,154,157,163-168) have been described. Some studies reported also a reduction of atherothrombotic profile paralleled by reduced incidence of cardiovascular accidents, an amelioration of cardiovascular and endothelial function, improved longevity of renal transplant (165) and a higher survival rates after islet transplantation in IAK recipients (162,165,169-173).

By combining donor selection criteria with improved isolation techniques and adequate immunomodulation of the recipient, insulin independence after single donor islet preparation is becoming more reproducibly possible to achieve. Islet preparations obtained from more than one donor pancreas can be transplanted at once after pooling them, or sequentially based on the metabolic needs of each subject. Data from the Clinical Islet Transplant Registry and independent trial reports have shown that insulin independence at one year from completion of the transplant is up to 70% with virtually 100% of the subjects maintaining graft

function (c-peptide) if adequately immunosuppressed (75,82). A progressive loss of insulin independence with approximately 90% of subjects requiring reintroduction of exogenous insulin (most of them with detectable c-peptide) has been reported in recent clinical trials based on the 'Edmonton protocol' (induction with anti-IL2R antibody; maintenance with sirolimus and tacrolimus) and some variants of it (60,77,84,86,174). More recent trials using more potent lymphodepletion (i.e., thymoglobulin, anti-CD3 or anti-CD52 antibodies) and/or biologics (anti-IL2R, anti-TNF, anti-LFA-1 antibody or CTLA4Ig) have shown great promise with approximately 50% of insulin independence at 5 years after islet transplantation (86,175-179), which is comparable to some of the data in whole pancreas transplantation in subjects with Type 1 Diabetes (80,83,86,91,92). In light of the results of the last decade of clinical islet transplant trials, achievement of insulin independence, although desirable, no longer should be considered the main goal of islet transplantation. The sizable improvement of metabolic control in the absence of severe hypoglycemic events, the amelioration of diabetes complications and the achievement of sustained better quality of life, which are quite cumbersome to reproduce by the means of medical treatment, justify the risks associated with the islet transplant procedure and immunosuppression in this high-risk population of subjects with unstable diabetes.

Regarding auto transplantation the largest published series are from the University of Minnesota (16-19), University of Cincinnati (20,21), and Leicester (22-25,180). Overall, one-third of patients in the Minnesota series achieves insulin independence, and the majority have islet graft function, as documented by C-peptide positivity (16,22). Cincinnati, Leicester, and other centers have published similar results, with 22-40% of the patients being insulin independent after islet transplant (21,181,182). A significant association between insulin independence and the IEQ/kg transplanted (i.e., islet mass standardized by patient's weight) was described. Bellin et al. (19) and White et al. (24) reported that insulin independence is related to the number of transplanted islet cells (>2,000 IEQ/kg and >3,000 IEQ/kg, respectively). Similarly, Sutherland et al. (183) reported that insulin independence at 1 year was observed in 63 % of the patients who received greater than 5,000 IE/kg. Moreover, pancreatectomy recipients benefit from an islet autograft ways apart from insulin independence. In fact, the major goal of IAT in these patients is a good glycemic control without brittle diabetes. Ninety percent of patients in the Minnesota series and 100% of those in the Leicester series were C-peptide positive after the procedure (16,22). The majority of patients receiving an islet auto transplant maintained good glycemic control, with 82% of all recipients having average HbA1c levels <7.0% (16).

IMPACT OF ISLET TRANSPLANTATION ON DIABETES COMPLICATIONS

Encouraging results have been reported in recent years on the multiple beneficial effects of islet transplantation on the progression of diabetes complications [reviewed in (184)]. Although based on nonrandomized pilot studies, which should be cautiously evaluated, they provide the proof of concept of the importance of restoring beta-cell function in patients with diabetes. In particular, improvement of micro- and macro-angiopathy (main causes of diabetic nephropathy) (79,101,102,154,157,163-168) and stabilization/reduced progression of retinopathy (104,157-159) and neuropathy (158,160-162) have been described. Amelioration of cardiovascular and endothelial function, reduction of atherothrombotic profile paralleled by reduced incidence of cardiovascular accidents and higher survival rates were reported In IAK recipients (169-172) (162,165,169,171,173). Furthermore, significantly improved longevity of a renal transplant was observed after islet transplantation (165). It is likely that these benefits are the consequence of improve

metabolic control conferred by the islet transplant. In addition, it has been proposed a contribution of restored c-peptide secretion and its effects on multiple targets (185).

Table 6. Benefits of Islet Transplantation
Metabolic control - Reduction of exogenous insulin requirements or insulin independence - Reduction of MAGE - Reduction or normalization of A1c - Absence of severe hypoglycemia
Quality of Life - Reduced fear of hypoglycemia - Improvement of Diabetes Quality of Life
Diabetes complications - Improvement of micro- and micro-angiopathy - Improvement of cardiovascular and endothelial function - Reduced incidence of acute cardiovascular events - Reduced nephropathy progression - Stabilization/slower neuropathy progression - Stabilization/slower retinopathy progression

COMMON ADVERSE EVENTS AND THEIR MANAGEMENT (TABLE7)

The procedure of islet transplantation has proven to be very safe, especially when compared with whole pancreas transplant (177,186,187). For allogenic islet transplantation bleeding, either intraperitoneal or liver subcapsular, is the most common procedure-related complication, occurring with an incidence as high as 13% (188). The use of fibrin tissue sealant and embolization coils in the hepatic catheter tract seems to effectively minimize the bleeding risk (188,189). Partial portal vein thrombosis complicates fewer than 5% of islet infusion procedures (174), and complete portal venous thrombosis is rare. The use of purer islet preparations, greater expertise in portal vein catheterization and new radiological devices (catheters medicated with anticoagulation) will continue reducing the risk of portal vein thrombosis, although the risk is unlikely be completely eliminated. Other complications of islet cell transplantation include transient liver enzyme elevation (50% incidence) (106), abdominal pain (50% incidence), focal hepatic steatosis (20% incidence) (190,191), and severe hypoglycemia (< 3% incidence). Another complication related to the intrahepatic islet transplantation procedure is portal hypertension that can occur acutely during the islet infusion, especially in the case of infusions other than the first one (192). Finally, severe hypoglycemia is a risk associated with the infusion of islets. Iatrogenic hypoglycemia in the immediate post-transplant period is a rare event. Frequent blood glucose monitoring immediately following islet transplantation is recommended to

avoid severe unrecognized hypoglycemia in the early post-transplant period. The risk of transmission of CMV disease from donor to recipient has been surprisingly low in recipients of islet allografts, particularly in the most recent period with routine use of purified islet preparations (140-144). As with any allogeneic transplant, islet transplant recipients may become sensitized to islet donor histocompatibility antigens (HLA), leading to the development of panel reactive alloantibodies (PRA).Data on the development of cytotoxic antibodies against donor HLA in islet allotransplant recipients with failing grafts have been reported from several islet transplant centers (148-152). A potential consequence of high PRA levels in recipients of a failed islet transplants is that if these individuals develop diabetic nephropathy in the future, a high PRA may increase their time on a transplant list for a suitable kidney graft.

The need to implement anti-rejection therapy exposes transplant recipients to an increased risk of untoward side effects expected in any immunosuppressed subjects (Table 6) (107). Opportunistic infections of urinary tract, upper respiratory tract and skin are frequent, along with myelosuppressive and gastrointestinal effects of the immunosuppressive drugs. In the majority of the cases, these effects are not severe and resolve without sequel with medical treatment. Elevation of viremic titers for cytomegalovirus (CMV) or Epstein-Barr virus (EBV) in the presence of overt clinical symptoms (*i.e.*, *de novo* infection or reactivation in seropositve subjects) imposes the implementation of anti-viral therapy and reduction of immunosuppressive drug dose (98). Timely intervention may result in faster resolution of the symptoms without compromising graft survival. Direct organ toxicity of immunosuppressive drugs has been recognized. Symptoms associated with neuro- and/or nephro-toxicity are relatively frequent in subjects receiving chronic immunosuppressive agents currently in use in the clinical arena. In these cases, modification of the anti-rejection regimen is indicated, with dose reduction or conversion to a different combination of drugs. In the majority of cases, these changes resolve the symptoms without compromising graft survival (193,194). Nephrotoxicity from sirolimus and/or tacrolimus has been described in patients with T1D undergoing islet transplantation, particularly when kidney function is already impaired because of pre-existing diabetic nephropathy (195,196).

As for the CITR 11th Allograft Data Report Scientific Summary, the decline in eGFR (CKD-Epi) after islet transplantation is both statistically significant and clinically important. IAK had much lower pre-transplant levels than ITA, which then declined at a slower rate. Initial levels were also lower in recipients age 35 and older and declined at a slower rate compared to younger recipients. Levels were generally lower among recipients managed with CNI+IMPDH compared to other maintenance immunosuppression regimens. Compared with an age-unadjusted cohort of 1,141 participants with T1D followed by the Diabetes Control and Complications Trial and then by the Epidemiology of Diabetes Interventions and Complications (EDIC) (The DCCT/EDIC Research Group, 2011) who started with mean eGFR levels of 126 ml/min/1.73m3, CITR allograft recipients had much lower mean eGFR (91±1SE for ITA and 62±2 for IAK) at their first transplant. CITR ITA recipients exhibited a decline in eGFR of 12 ml/min/1.73m3 and IAK experienced a mean decline of 2 ml/min/1.73m3 in 5 years from last infusion, compared to a mean decline of about 9 ml/min/1.73m3 over the first 5 years in the DCCT.

As of 2021, by decision of the Executive Committee, only serious adverse events (SAEs) are reportable to CITR. About 11% ITA and 14% of IAK allo-islet recipients experienced a serious adverse event in the first 30 days following transplantation. There was a sharp decline in the number of patients who experienced SAEs post-2010, with 15% or more of patients experiencing SAEs in early eras compared

to ~5% in 2011-2014 and 2015-2018. In the first year after islet transplantation, which includes a majority of the reinfusions that were performed, about one-fourth of participants have experienced an SAE. SAE within 1-year was slightly more common in IAK (31%) than ITA (23%) and there was a significant decline post-2010 (>25% pre vs. <15% post). Life-threatening events have occurred in 13.4% of islet-alone, in 16.5% of IAK recipients, and in 20.4% of SIK recipients. Recent eras have seen a substantial decline in the incidence of life-threatening events. The most common life-threatening events reported were abnormal granulocytes (24 events) followed by abnormal liver function (23 events) and hypoglycemia (14 events). About 75% of patients who experienced a life-threatening event recovered fully, 12% recovered with sequelae, 5% did not recover, and 9% died as a result of the event.

A total of 189 instances of neoplasm have been diagnosed in 101 of the 1,399 islet recipients who collectively represent a total of 7,963 person-years of observed follow-up. This equates to about 0.02 neoplasms per person-year. Of the total 189 events, 61% were deemed possibly related to immunosuppression, and 12% definitely related. Of the total events, 69% recovered, 10% did not recover, 5% recovered with sequelae, and 3% resulted in fatality. There were 41 instances in 23 patients of basal carcinoma of the skin and 86 instances in 38 patients of squamous carcinoma of the skin. There were 56 instances in 39 recipients of non-skin cancers. Eleven deaths due to cancer occurred.

There have been 77 or 5.5% deaths; cumulative mortality rates differed significantly by transplant type ($p<0.0001$) but not by era. SIK transplant recipients were disproportionately represented among fatalities comprising only 3.5% of the allo-islet recipient population, but 15.6% percent of deaths. Of the reported deaths, ten were deemed possibly related or definitely related to islet transplantation or immunosuppression. The most common causes of death were (# cases): cardiovascular (15), neoplasm (11), infection (including pneumonia) (9), hemorrhage (4), and complications of diabetes (3). Twenty-four deaths did not have a cause specified.

An assessment of the surgical complication of islet auto transplantation was recently reported for the entire Minnesota series (n=413) (16). Surgical complications requiring reoperation during the initial admission occurred in 15.9% of the patients. The most common reason for reoperation was bleeding, occurring in 9.5% of the procedures. Anastomotic leaks occurred in 4.2 % of the patients, biliary in 1.4% and enteric in 2.8%. Intra-abdominal infection requiring reoperation occurred in 1.9% of patients, wound infections requiring operative debridement in 2.2%. Gastrointestinal issues, such as bowel obstruction, omental infarction, bowel ischemia, delayed reconstruction because of bowel edema, tube perforation, requiring reoperation in 4.7% of the patients. Two patients (<1%) required reoperation to remove an ischemic or bleeding spleen after spleen sparing pancreatectomy (done in 30% of patients).

Table 7. Most Frequent Complications in Islet Transplant Recipients

Procedure-related
- Hemorrhage - Portal thrombosis - Transient transaminitis
Immunosuppression-related

Hematological

- Anemia
- Leucopenia
- Neutropenia

Metabolic

- Dyslipidemia

Gastrointestinal

- Oral ulcers (Sirolimus)
- Diarrhea (Mycophenolic acid)
- CMV colitis

Respiratory tract

- Upper respiratory infections
- Interstitial pneumonitis (Sirolimus)

Neurological

- Neurotoxicity (Tacrolimus)

Genitourinary

- Urinary infections
- Ovarian cysts
- Dysmenorrhea
- Nephropathy
- Proteinuria

Cutaneous

- Infections
- Cancer

CURRENT CHALLENGES

There are many challenges that are currently limiting islet cell transplantation (Table 8) (197-199) While significant progress has been made in the islet transplantation field, several obstacles remain precluding its widespread use. The clinical experience of islet transplantation has been developed almost exclusively using the intra-hepatic infusion through the portal vein (60). It has been suggested that the loss of as many as 50-75% of islets during engraftment is the reason why a very large number of islets are needed to achieve normoglycemia (51,72). Moreover, two additional important limitations are the currently inadequate immunosuppression for preventing islet rejection (70) and the limited oxygen supply to islet in the engraftment site (200,201). Current immunosuppressive regimens are capable of preventing islet failure for months to years, but the agents used in these treatments may increase the risk for specific malignancies and opportunistic infections. In addition, the most commonly used agents (like calcineurin inhibitors and rapamycin) are also known to impair normal islet function and/or insulin action. Furthermore, like all medications,

these agents have other associated toxicities, including the harmful effect of certain widely employed immunosuppressive agents on renal function. The second very significant factor for early and late loss of islet mass is the critical lack of immediate vascularization and chronic hypo-oxygenation. Physiological supply of oxygen and nutrients in native islets is maintained by a tight capillary network, destroyed by the islet isolation procedure, restricting supply to diffusion from the portal vein and hepatic arterial capillaries until the revascularization process is completed. Oxygen tension in the liver parenchyma decreases from approximately 40 to 5 mmHg, eight-fold lower compared to the intra-pancreatic levels, leading to severe hypoxia, and β-cell death. Revascularization of the islet graft in rodent transplant requires 10-14 days and much longer in non-human primates and human recipients. Even after the revascularization of the islets is completed, the capillary' density is significantly lower compared to the physiological intra-pancreatic situation. Finally, one of the main challenges is the cost of the procedure and some regulatory issues, as recently demonstrated by the ongoing discussion in USA (202). In fact, on April 15, the FDA's Cellular, Tissue, and Gene Therapies Advisory Committee voted in favor of approval of the biologics license application (BLA) seeking to market allogeneic islets of Langerhans for the treatment of 'brittle" type I diabetes mellitus in adults whose symptoms are not well controlled despite intensive insulin therapy. The FDA endorsement of islet transplantation adds to the list of national agencies in Europe, such as the Federal Office of Public Health in Switzerland, the National Health Service (NHS) in the UK, the Swedish Local Authorities and Regions, the Ministry of Health in Poland and Belgium and, more recently, the French National Authority for Health (HAS) in France that have approved islet transplantation as a reimbursed standard-of-care procedure. Unfortunately, the FDA has chosen to consider islets as a biologic that requires licensure, making the universal implementation of the procedure in the clinic very challenging.

Table 8. Current Challenges Faced for Islet Transplantation

Challenge	Possible impact	Potential solutions
Progressive graft dysfunction	Reintroduction of exogenous insulin; Destabilization of metabolic control; Supplemental islet transplant.	Incretin mimetics; Alternative islet implantation sites; Novel immunosuppressive protocols.
Multiple islet donors	Increased operational costs; Shortage of deceased donor pancreata for transplantation; Risk of allosensitization.	Improved donor selection criteria; Optimized cell processing; Alternative sources of transplantable tissue (i.e., stem cells-derived or xenogeneic islets; Alternative implantation sites.

Chronic immunosuppression	Systemic toxicity; Increased risk of opportunistic infections; Islet cell toxicity.	Use of biologics; Immune isolation techniques; Development of immune tolerance inducing protocols.
Allosensitization	Reduced graft survival; Preclude/worsen outcome of subsequent transplantation (i.e., islet or renal)	Maximizing the success rate of single donor islet transplantation; Alternative sources of transplantable tissue; Immune isolation; Plasmapheresis / depletion of alloantibodies; Novel immunosuppressive protocols; Development of immune tolerance inducing protocols.
Cumbersome graft monitoring	Mainly rely on metabolic function tests, but cannot discriminate between immunological and metabolic causes of dysfunction; Liver needle biopsies do not provide adequate graft tissue; MRI and PET lack the resolution to detect islets scattered throughout the liver.	Improved simple metabolic measures predictive of graft dysfunction; Improved sensitivity of noninvasive imaging techniques (functional MRI?); Improved immune monitoring techniques for early detection of immune events able to discriminate between rejection and autoimmunity.

FUTURE DEVELOPMENTS IN BETA-CELL REPLACEMENT THERAPIES

The field of cellular therapies for the treatment of diabetes is rapidly evolving and a new exciting era has already begun (shown in Fig. 1). Efforts are ongoing to push to a broader dimension islet transplantation (143), including: (i) implementation of a scheme for donor and recipient selection and organ allocation to increase pancreas utilization (203-205); (ii) improvement and standardization of islet isolation process and its best codification by regulatory bodies (206-209) (iii) monitoring of transplanted islets by noninvasive imaging techniques (210,211); (iv) development of biomarkers to assess the efficacy of the immunosuppression/immunomodulation

strategies (69,212-216); (v) identification of alternative transplantation sites (51); (vi) creation of an ideal bio-artificial niche for islet survival by bioengineering approaches (217,218) and (vii) use of immune-isolation techniques, such as hydrogel polymers that shield pancreatic islet from immune cell attack (219,220). On the other hand, there is increasing new excitement for the use of ***unlimited alternative sources of transplantable islets***, such as **xenogeneic** (i.e., obtained from other species such as porcine islets) [reviewed in (221)] or derived from human **stem cells (222-227)**. Pig islets may be available in plentiful amounts. Importantly, the ability to obtain genetically modified pigs that lack or overexpress specific molecules may be of assistance in developing cellular products with reduced immunogenicity for transplantation into humans. In turn, this technology may allow achieving long-term function under immunosuppressive regimens that are used for allogeneic cells or facilitating the induction of long-term acceptance of xenogeneic islet cells. Another area reporting great progress is that of regenerative medicine using human stem cells from embryonic or adult sources.

While adult stem cells, such as mesenchymal stem cells, have an immunomodulatory potential when infused at disease onset (228) (229) or as adjuvants to improve the outcomes of islet transplantation (230), the greatest enthusiasm lies in the possibility to use pluripotent stem cells to overcome the limits of islet transplantation (231,232). Human pluripotent stem cells (both embryonic stem [ES] and induced pluripotent stem [iPS] cells), are the best candidate for making β cells as they have unlimited potential for division and differentiation. Efficient protocols for the differentiation of pluripotent cells into β cells have been developed by several laboratories (233-241) and a great effort in the last year was concentrated on developing cellular products with consistent potency and safety profile for clinical application. Actually, six clinical trials using human pluripotent stem cells for the therapy of type 1 diabetes are registered in ClinicalTrial.gov: three active and recruiting (NCT03163511; NCT04678557; NCT04786262), one completed (NCT03162926), one enrolling by invitation (NCT02939118) and one active but not recruiting (NCT02239354). All these trials, except the NCT04786262, are using PEC-01 cells as a cell product. PEC-01 cells are a mixed cell population comprising pancreatic endoderm and poly-hormonal endocrine cells (233,242,243) differentiated by a pluripotent stem cell line called CyT49 (225). These pancreatic precursor cells are fully committed to further differentiate into mature endocrine pancreatic cells after their implantation and were tested within an encapsulation device in subcutaneous space. In December 2021, the interim results of some of these clinical trial appeared in two articles (244) . Over the follow-up period, which lasted up to 1 year, patients had 20% reduced insulin requirements, spent 13% more time in target blood glucose range, had stable average HbA1c <7.0%, had improved hypoglycemic awareness (average Clarke score decreased ~1 point) associated with C-peptide levels that were, on average, ~1/100th normal levels. Explanted grafts contained heterogeneous composition of pancreatic cells, including cells with mature β cell phenotype. In both the papers: (i) induction and maintenance immunosuppression appeared to be effective in preventing allogeneic and autoimmune destruction of the graft cells, (ii) the cell product appeared to be safe and well tolerated, since no teratoma formation was observed and the great majority of mild-to-moderate adverse effects was due to surgical procedure risks and side-effects of immunosuppression. These initial data reinforce the hope that pluripotent stem cells, differentiated into pancreatic endocrine cells, may be a renewable source of β cells for patients with T1D.

VX-880 is a second cell product approved in 2021 as investigational cell therapy for the treatment of type 1 diabetes. VX-880 consists of fully differentiated insulin-producing pancreatic islet cells obtained from

pluripotent stem cells. A Phase 1/2, single-arm, open-label clinical trial was recently approved in patients who have T1D with impaired hypoglycemic awareness and severe hypoglycemia. VX-880 is infused in the portal vein and a chronic administration of concomitant immunosuppressive therapy is be required to protect the islet cells from immune rejection. Some preliminary results have already been shared in a press release in May 2022 and suggest that β cells fully differentiated from stem cells and transplanted into the liver may engraft and start secreting insulin early after infusion. In addition to ongoing clinical experiences, others commercial or academic organizations have announced their intention to conduct clinical trials of functional stem cell derived-islets (135). At this point, the need to shield the transplanted stem-cell-derived β-cells from immune rejection becomes more and more critical. In this direction, different strategies to reduce or avoid immune rejection are under evaluation (245) including (i) generation of universally compatible pluripotent stem cells by silencing or deleting HLA or genes essential for HLA expression or function and by expressing genes encoding immunosuppressive molecules (246), (ii) development of mild immunosuppressive regimens (e.g., monoclonal antibodies targeting NK cells and/or T cell subsets) sufficient to induce tolerance, (iii) improvement in encapsulation/containment of cell product and (iv) creation of a haplobank of stem cell lines (247).

A current limitation for islet transplantation is the inability to use non- or minimally-invasive predictive tests as well as biomarkers of early graft dysfunction to guide timely interventions aimed at preserving functional islet cell mass. ***Metabolic tests*** (*i.e.*, glycemic control, insulin requirement, HbA1c, basal and stimulated c-peptide) remain the main indicators of graft function, the alteration of which may indicate underlying distress of the graft but cannot discriminate possible causes such as metabolic overload, immunity, or drug toxicity. In some cases, graft dysfunction may be reversible (*i.e.*, transient metabolic overload due to an infection episode), but in many other cases at the time graft dysfunction is detected, a considerable mass of functional beta cells might already be irreversibly lost. Monitoring of transplanted islets by ***noninvasive imaging*** techniques (such as MRI, PET-CT, and US) is cumbersome, as they lack the resolution for the detection of cellular clusters the size of islets (~50-900um) that are scattered throughout the recipient's liver [reviewed in (248)]. While encouraging preliminary studies have shown that preloading of aliquots of the islet graft with iron nanoparticles (for MRI) (249-253) or labeled glucose (for PET-CT) (254-257) can be used safely, these techniques do not allow assessing the whole mass of transplanted clusters and provide only passive and transient information on islet distribution in the transplant site. The progress in the field of functional MRI (fMRI) and toward the development of more sensitive beta-cell specific imaging techniques may allow a more objective assessment of islet cell mass over time in a near future. Detection of ***biomarkers*** [reviewed in (109)] in blood samples to determine immune cell function (*i.e.*, cell surface expression of specific markers by flow cytometry and cytotoxic lymphocyte gene expression profiles, amongst other)(258-260) and autoimmunity reactivation (namely, autoantibody titers) is evaluated in ongoing clinical trials to identify means of assessing the efficacy of the immunomodulation strategies, detecting rejection episodes and reactivation of autoimmunity early enough to implement timely immune interventions to prevent graft loss (69,70,261-263). Unfortunately, some of the current tests lack adequate specificity as they may be affected also with underlying infections. With the rapid evolution of high throughput arrays, it is likely that new and more specific molecular biomarkers of islet cell distress and immune cell function will become available in the near future. ***Alternative transplantation sites*** [reviewed in (51)] are being currently explored that may contribute enhancing islet engraftment and attain sustained graft function long-term (52). Importantly, alternative

sites may be modified using bioengineering approaches that could enable creating an ideal bio artificial endocrine pancreas [reviewed in (264)]. The use of ***immunoisolation*** techniques, such as using hydrogel polymers that shield islet cell clusters from immune cell attack, may contribute to achieve sustained function of transplanted cells without the need for life-long immunosuppression [reviewed in (265) and (264)].

CONCLUSIONS

In conclusion, islet transplantation as it is today cannot be the universal cure for type 1 diabetes. It represents a clinical option in few highly selected patients but it is the proof of principle that it is possible to replace efficiently β cells in patients with diabetes by a cell therapy. Restoration of physiologic metabolic control in patients with diabetes is highly desirable. Transplantation of islets of Langerhans allows the achievement of stable metabolic control in the most severe manifestations that cannot be matched with conventional medical therapies. The steady progress of clinical islet transplantation and the promising emerging new approaches that address immunity and beta cell sources justifies cautious optimism for the potential applicable of beta-cell replacement to all cases of insulin-dependent diabetes in the near future.

ACKNOWLEDGMENTS

This work was partially supported by the Italian Minister of Health (Ricerca Finalizzata RF-2009-1483387, RF-2009-1469691), Ministry of Education, University and Research (PRIN 2008, prot. 2008AFA7LC), Associazione Italiana per la Ricerca sul Cancro (AIRC, bando 5 x 1,000 N_12182 and Progetto IGN_ 11783), EU (HEALTH-F5-2009-241883-BetaCellTherapy) and the Juvenile Diabetes Research Foundation International.

The author alone is responsible for reporting and interpreting these data; the views expressed herein are those of the author and not necessarily those of the funding agencies.

ONLINE RESOURCES ON THE SUBJECT

Clinical Islet Transplant Consortium; Collaborative Islet Transplant Registry; Diabetes Research Institute Foundation; Health Resources and Services Administration; International Pancreas & Islet Transplant Association; The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK); Organ Procurement and Transplantation Network; The Cell Transplant Society; Scientific Registry of Transplant Recipients; United States Department of Health and Human Services; United Network For Organ Sharing (UNOS).

ADDITIONAL ONLINE RESOURCES IN RELATED TOPICS

American Diabetes Association; American Society of Transplantation; American Society of Transplant Surgeons; Beta Cell Biology Consortium; European Pancreas Club; European Society for Organ Transplantation; International Pancreas Transplant Registry; International Xenotransplantation Association; Juvenile Diabetes Research Foundation.

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