

Transplantation: current developments and future directions; The future of clinical islet transplantation as a cure for diabetes

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1. ABSTRACT

Islet transplantation is now a therapeutic option for patients with unstable type 1 diabetes mellitus (T1DM) with hypoglycemic unawareness. The benefits of this treatment include improvement in metabolic control with normalization of A1c and prevention of severe hypoglycemia. Insulin independence and improved quality of life can be reproducibly obtained by transplanting adequate islet numbers. Current obstacles to the widespread application of beta-cell replacement therapies include limited islet availability and the need for chronic immunosuppression. The emergence of promising interventions may be of assistance in improving islet recovery and favoring engraftment of smaller islet masses with comparable or better efficacy. In the future, regenerative efforts will contribute to overcoming this limitation as well. Combining these approaches with the development of safe immune interventions to induce self tolerance or to induce the permanent acceptance of transplanted tissues will be necessary to achieve long-term success. The steady progress and promising results of recent clinical trials justifies a great optimism toward the widespread application of beta-cell replacement as a treatment of choice for patients with diabetes.

2. INTRODUCTION

The steady progress of beta-cell replacement strategies in the clinical setting and the new therapeutic options emerging from the experimental setting are quite encouraging (1, 2). Replacement of beta-cell function may be of assistance in the restoration of physiologic metabolic control and thereby reduce the risk of progressive diabetic complications in patients with T1DM. Transplantation of islet beta-cells by implantation of vascularized pancreata or isolated islets has proven effective in recent clinical trials (3).

The islets of Langerhans are endocrine cell clusters that represent approximately 1% of pancreatic tissue (4). Each islet contains different cell subsets specialized in the production and secretion of the hormones (alpha-cells: glucagon; beta-cells: insulin; delta-cells: somatostatin; PP-cells: pancreatic polypeptide) that control glucose metabolism within the physiologic range. In type 1 diabetes mellitus (T1DM), an autoimmune destruction of pancreatic beta-cells leads to insulinopenia with consequent hyperglycemia and ketoacidosis. Standard treatments, which include diet, exercise and exogenous insulin, cannot replace the physiologic control provided by the beta-cells.

Nonetheless, aggressive insulin administration has proven effective in delaying as well as preventing the onset of dreadful diabetic complications (*i.e.*, neurologic, ophthalmologic, cardiovascular, renal and metabolic) in patients with T1DM (5). The underlining risks of an intensive insulin regimen include life-threatening hypoglycemia, particularly in patients who have lost the autonomic warning symptoms associated with hypoglycemia (4).

3. CLINICAL ISLET TRANSPLANTATION

3.1 Current indications

Transplantation of pancreatic islets was first performed in patients with surgically-induced diabetes (*i.e.*, pancreatectomy for the palliative treatment of pain secondary to chronic pancreatitis) as autologous intrahepatic islet transplantation (islet autotransplantation) (6). Encouraging outcomes have also been observed in recipients of allogeneic islets (islet allotransplantation) in patients without autoimmune diabetes (7).

The main indication for allogeneic islet transplantation is T1DM. This therapeutic option is offered to patients with imminent or end-stage renal disease (ESRD) who have received or will receive a kidney transplant (islet transplantation simultaneous or subsequent to kidney transplantation) (8). Additionally, islet transplantation can be considered for patients with preserved renal function who have a history of severe and acute metabolic complications requiring medical attention (*i.e.*, hypoglycemia, hyperglycemia and ketoacidosis) and/or clinical and emotional problems with exogenous insulin therapy that are incapacitating and/or consistent failure of insulin-based management to prevent diabetic complications (8).

3.2. Islet processing

Pancreatic islets are isolated from the donor pancreas using a mechanically-enhanced enzymatic digestion procedure. The goal of this process is to fragment the pancreatic gland while preserving islet cell cluster integrity using a dissociation chamber in a closed circuit (9). The digestion phase is followed by a purification step that enriches the endocrine fraction (10, 11). This step reduces the contaminating non-endocrine tissue and minimizes the final volume of the pancreatic digest to be transplanted.

Despite the numerous technological improvements of recent years, the efficiency of islet cell processing yields a mass that is significantly less than the estimated mass of endocrine tissue present in a human pancreas (approximately 40-50%) (12). This may be the consequence of multiple factors which include donor-related variables (age, weight, cause of death, etc.), pancreas recovery and preservation techniques, ischemia time and the isolation process. In addition, the donor pancreas itself, due to the peculiar susceptibility of the pancreas to noxious insults, unleashes the activation of enzymes that result in autolysis of the gland. The combination of these insults may lead to the reduction of

the quality and quantity of islets recovered. Notably, the need for multiple donor glands per recipient is generally observed in the clinical setting, representing one of the major limitations of islet transplant due to the shortage of donor organs.

3.3. Transplant procedures

Islet preparations with variable degrees of endocrine fraction purity (between 30-90% pure islets) are implanted into the recipient liver sinusoids via portal vein infusion. The transplant procedure is currently performed as a percutaneous, transhepatic cannulation of the portal vein under sonographic and fluoroscopic guidance (7, 13-15). This procedure has been associated with low morbidity and no mortality (14-17). When transhepatic access is contraindicated, a tributary of the portal system is cannulated *via* mini-laparotomy or *via* laparoscopic intervention (18).

3.4. Post-transplant metabolic monitoring

Transplantation of allogeneic pancreatic islets is performed in patients with stimulated C-peptide levels of ≤ 0.3 ng/ml, so that graft function can be monitored by measuring C-peptide in the blood (19, 20). Additionally, graft function is monitored by assessing exogenous insulin requirements, glycated hemoglobin (A1c), fasting and postprandial glycemic values, and mean amplitude of glycemic excursions (MAGE) as well as by the means of metabolic tests at baseline and periodically during the follow up. These include intravenous and oral glucose tolerance tests complemented with arginine stimulation and mixed meal tolerance tests to estimate glucose clearance and insulin (and C-peptide) release during metabolic challenge (18, 20-22). Metabolic tests are relatively sensitive tools for the monitoring of graft function but require a cumbersome set-up and significant patient compliance. More practical management tools include the monitoring of basal glycemic and C-peptide values to estimate graft function (*i.e.*, C-peptide to glucose ratio). This could provide critical data that is less taxing to the transplanted patients and useful to detect the onset of graft dysfunction in order to take appropriate measures (20). Furthermore, useful algorithms to estimate clinical outcome after islet transplantation include the 'Ryan beta-score' that accounts for glycemic control, diabetes therapy and endogenous insulin secretion. This scoring system correlates well with measures of beta-cell function (23). Post-transplant monitoring also includes assessment of the impact of beta-cell replacement on the frequency and severity of hypoglycemic events (21, 24).

3.5. Clinical outcomes

Recent clinical trials have shown the significant benefits of replacing beta-cell function by allogeneic islet transplantation. These include improvements in glycemic control with normalization of A1c and substantial reduction of insulin requirements after islet implantation (18, 25-45). Insulin independence is reproducibly attained by transplanting an adequate islet mass (approximately 13,000 IEQ/kg of recipient's body weight), and generally using more than one donor pancreas per recipient. Insulin independence can be observed following single donor islet

transplantation (35, 36, 46), but generally requires sequential or pooled islet preparations obtained from two to three donor pancreata (28, 30, 35, 36, 47, 48). A dramatic reduction in insulin requirements and MAGE is generally observed after the first islet infusion, often paralleled by a normalization of A1c (28, 30, 35, 36, 38, 48). After completion of the infusion protocol and achievement of insulin independence, glycemic profiles normalized in most cases (28, 30, 35, 36, 48) as documented by the use of continuous monitoring systems (38).

One of the major benefits of islet transplantation is the impact on severe hypoglycemia that can be prevented even when exogenous insulin is required to maintain adequate glycemic control (28, 30, 35, 36, 48). This phenomenon has been associated with a restoration of normal suppression of glucagon by hyperinsulinemia during euglycemic clamps (49). Although lack of hypoglycemic hormonal counterregulation and autonomic symptom recognition during hypoglycemic clamp studies has been reported (50), new evidence of normalization of glycemic thresholds for activation of counterregulatory hormone and symptom response has been presented, despite the persistence of impaired glucagon and epinephrine responses during hypoglycemia (51). Interestingly, prevention of severe hypoglycemia can persist long-term as long as residual graft function is present (18, 19). Both improved glycemic metabolism and absence of severe hypoglycemia have a beneficial impact on the quality of life of islet transplant recipients (52-54).

The potential benefits of islet transplantation on diabetic complications are currently under evaluation. Initial promising data on small cohorts of patients justify a cautious optimism. Improved cardiovascular and renal function, as well as improvements in symptoms related to neuropathy and retinopathy, have been reported following islet transplantation (55-59). Future randomized clinical trials on larger patient cohorts will be of assistance in determining the real impact of islet transplantation on the progression of diabetes-related complications.

3.6. Complications

Intrahepatic islet infusion is associated with low morbidity (14-17, 36, 60-64). Bleeding has been the most common procedural complication reported followed by portal vein thrombosis (17). However, advances in islet infusion techniques (7, 14, 65), intrahepatic catheter tract coagulant techniques (15, 36) combined with the use of peri-procedural anticoagulation (36) make these complications completely preventable. In addition, islet graft function has not been affected by procedural morbidity. The use of chronic immunosuppression bears intrinsic side effects that are expected based on the safety profile of the drugs commonly utilized in ongoing clinical trials. An increased frequency of upper respiratory and urinary tract infections is commonly seen in immunosuppressed patients. Tacrolimus-associated side effects have included neurotoxicity (64, 66), nephrotoxicity and cutaneous complications (67) that in selected cases require conversion to other immunosuppressive drugs (*i.e.*, mycophenolic acid) (68). Sirolimus has led to the

generation of oral ulcers generally at the initiation of the treatment, as well as interstitial pneumonia and dyslipidemia requiring medical treatment (64). Sirolimus-induced colitis has been observed in association with supra-therapeutic trough levels (69). An increased incidence of ovarian cysts was observed in islet transplant recipients treated with sirolimus and tacrolimus (70). Development of proteinuria has also been described in patients with impaired glomerular filtration and/or microalbuminuria before initiation of immunosuppression (45, 71-74).

Allosensitization in recipients of allogeneic solid organs has been associated with poor graft outcomes (75). In the case of islet allotransplantation, the data remains inconclusive as to whether allosensitization can influence graft outcome (27, 47, 76-80). In recent trials, allosensitization was not common in patients under immunosuppression (30, 35, 36, 48, 79, 80), while it was observed consistently after discontinuation of immunosuppression in recipients of islet transplant alone (81). Although the actual impact of allosensitization in islet transplant recipients is currently unclear, a concern that it might preclude or adversely affect the outcome of future allogeneic transplants is warranted.

4. OVERCOMING CURRENT CHALLENGES THROUGH TRANSLATIONAL RESEARCH

4.1. Increasing islet availability

There is an urgent need for the definition of ways to improve islet recovery from a single human donor pancreas and to maximize utilization of donor organs for transplantation (82). This could be achieved by the implementation of stricter donor selection criteria (83, 84), introduction of more aggressive donor management before organ recovery (82), standardization of peri-surgical recovery techniques that favor pancreatic integrity (84), and improved organ preservation methods (85-87).

Islet cell processing has steadily improved thanks to the availability of more efficient dissociation enzymes (88, 89) and reagents that contribute to the preservation of islet mass during the isolation procedure (90). Major efforts are currently being focused toward the standardization of islet cell processing in order to obtain more reproducible results amongst centers (91, 92). To this aim, the concept of regional islet cell processing centers as part of 'islet consortia' represents an appealing option (94) as it has shown promise in recent clinical trials in Europe and the United States. This has allowed for better utilization of donor pancreata that may be shared between centers (40) as well as obtaining higher proportions of glands yielding adequate islet numbers for transplantation (82, 84). Development of safe shipping protocols between centers that allow for the preservation of functional integrity, viability and sterility during the transfer of islet cell products will contribute to a widespread application of the consortium in future years (93).

Expansion of the donor pool to include a greater utilization of organs from marginal donors and donors after cardiac death is possible as demonstrated by recent reports

(94-96). An additional avenue is the use of living-related donors (97, 98); however this should be considered only after a thorough evaluation of donor risks (99). Living islet donors may be possible when the currently observed progression to graft dysfunction in recipients treated with combined sirolimus and tacrolimus (35, 48, 78) is overcome with safer and more efficacious immune interventions.

From the preclinical standpoint, promising novel approaches are emerging in the areas of organ recovery, islet processing and cytoprotection. Lack of oxygen during islet isolation and subsequent culture triggers oxidative stress-induced intracellular pathways that lead to cellular functional impairment and death. Oxygen carriers (*i.e.*, neuroglobin and hemoglobin) (100, 101), perfluorocarbon-based preservation solutions (87), targeted anti-oxidative and cytoprotective molecules (*i.e.*, glutamine, superoxide dismutase mimic, carbon monoxide, beta-estradiol, heme oxygenase-1, *etc.*) (100, 102-106), ischemic preconditioning techniques (107, 108) and modulators of stress-activated protein kinases (*i.e.*, c-jun, MAPK) (109-111) are only a few of the interventions proposed to maximize organ quality.

4.2. Alternative sources of insulin-producing cells

The diabetes epidemic is a growing health care problem and an increasing number of patients would benefit from beta-cell replacement. Even if more human pancreata become available through the expansion of the donor pool and better utilization of currently available cadaveric organs is realized, the number would be insufficient to meet the high demand. To help solve this limitation, a number of potential sources of islet cells are currently being evaluated for future clinical applications.

Xenogeneic islets obtained from porcine donor pancreata are considered a potentially viable source as porcine and human insulin differ by a single amino acid. The ease of breeding and large availability of donor pigs would represent an unlimited and readily available source for islet transplantation in humans (112-115). Current hurdles encompass immune barriers and potential transmission of porcine endogenous retroviruses to immunosuppressed recipients (115). The generation of genetically engineered porcine strains with biochemical cell surface receptor modifications holds promise (116-121), but might not be sufficient to overcome the immune response against xenografts. In addition, the harsh immune interventions needed to preserve graft function in humans might not be suitable for patients with T1DM (122-125). A possible strategy to overcome these limitations is the implementation of immunoisolation strategies for xenogenic islets that could be of assistance at reducing the need for powerful systemic immunotherapies to prolong graft survival (126-129).

Great progress has been made in recent years to differentiate beta-cells from a wide variety of embryonic or adult stem cell subsets. Potential options to obtain insulin-producing cells *in vitro* include differentiation of mesenchymal (130, 131), hematopoietic (132) and

pancreatic ductal cell progenitors (134-136), as well as stimulating intra-islet precursors or replicating adult beta-cells (136). The differentiation potential of amniotic-derived stem cells is also appealing to this aim (137). Transdifferentiation of hepatocytes has been performed in experimental models and could represent an additional approach to generate insulin-producing cells (138-140). Expansion of adult human islets *in vitro* may represent another option. Currently, the efficiency of expansion and differentiation protocols is less than optimal. The proportion of functioning insulin-producing cells that have been obtained is marginal and far from physiologic (141, 142). The enormous progress of developmental biology and cell physiology will be a harbinger to new advances that may be applicable in the clinical arena in the near future.

4.3. Developing Predictive Islet Potency Tests

The limited success of islet transplantation in the past decade might have been due to the lack of predictive tests for the assessment of human islet cell products. This deficiency likely contributed to the high rates of transplanted islet primary non-function and the need for large islet numbers to attain insulin independence. Along with islet numbers, the most commonly used pre-transplant islet cell potency analysis has been through the use of viability tests using membrane-exclusion dyes and *in vitro* glucose-stimulated insulin release assessment (19, 143). Based on these methods, islet preparations with comparable quality and potency have yielded a very broad spectrum of outcomes, suggesting the poor predictive value of these tests on islet graft function after transplantation (143, 144). In order to overcome such limitations, there has been a massive effort in the islet transplant community to develop more sensitive assessments. A test that is able to accurately define the quality of human islet preparations for transplantation would identify suboptimal preparations that should not be transplanted, despite the availability of adequate islet numbers. Development of sensitive tests for the assessment of beta-cell specific viability in combination with beta-cell numbers in human islet preparations would theoretically provide a higher predictive tool than current methods. Experimental preliminary studies of islet transplantation in diabetic immunodeficient mice have shown the ability of such an approach to predict human islet cell potency *in vivo* (143). The translation of this model to the clinical setting is currently underway.

Measurements of the metabolic parameters of isolated islets via the assessment of oxygen consumption rates (145-147) and the ATP/ADP ratio (148) may add a supplementary insight into the well being of isolated islets. Therefore, a combination of tests that define the metabolic state, viability and functional competence of isolated human islets may yield a more stringent algorithm that will improve islet transplantation outcomes.

4.4. Enhancing islet engraftment

Multiple factors contribute to the high islet numbers required to attain insulin independence after islet transplantation. The generation of inflammation at the time of islet infusion into the hepatic portal system (islet-blood

interaction) (149, 150) and after embolization into the liver microenvironment (151), along with the lack of vascularization (and therefore of oxygenation) may contribute to the early functional impairment and loss of islet cell mass (152).

There is an ongoing effort to develop effective interventions able to reduce non-specific inflammation while favoring islet engraftment. Strategies proposed include the induction of cytoprotection to isolated islets to render them less susceptible to noxious stimuli in the early post-implantation period. Additionally, modulation of the inflammation at the site of implantation could enhance islet engraftment. Furthermore, accelerating neovascularization after implantation could prove effective in promoting islet cell mass engraftment as well.

Incretins or incretin analogues, such as glucagon-like peptide (GLP-1), are another possible intervention currently being tested (153, 154). Exenatide, a synthetic GLP-1 analogue already used clinically, has demonstrated an ability to reduce exogenous insulin requirements of patients experiencing delayed islet graft dysfunction (155, 156). In addition, the use of exenatide at the time of islet transplantation might be of help in preserving islet mass and favor engraftment. Clinical trials to test this possibility are currently underway.

Exploring alternative sites for islet implantation could alleviate the multiple stresses encountered at the islet implant microenvironment thereby favoring engraftment and long-term function. Over recent years, multiple sites have been tested. The use of the highly vascularized and portally drained omentum is an appealing islet transplantation site (157-162). A subcutaneous site has several advantages, including ease of access and peri-transplant monitoring, even though initial trials have yielded only partial success. Application of tissue engineering techniques to create a more suitable site for islet engraftment includes the use of pro-angiogenic factors to prevascularize the local microenvironment prior to islet implantation. Promising results have also been generated using implantable subcutaneous devices that allow for long-term function of islet tissue (163, 164). The encouraging success of these alternative sites in animal models could be transferred to the clinical arena shortly.

4.5 Refining post-transplant monitoring

A gold standard for the monitoring of islet mass and function has yet to be developed but would be an invaluable clinical resource to guide the management of patients who are status post islet transplant. Current monitoring techniques are invasive and physically taxing to patients. Furthermore, these tests cannot clearly and specifically assess beta-cell mass or discriminate between mass and function, even though sophisticated modeling may be of assistance in achieving a good approximation (165, 166). Development of non-invasive methods for a more accurate evaluation of beta-cell mass and function may help overcome the current limitations and offer the option of repeating the test to monitor changes in beta-cell mass over time. Emerging data suggests that monitoring of

insulin mRNA levels in the blood of islet transplant recipients in the peri-transplant period may represent a valuable tool since its elevation is associated with loss of islet cells soon after intrahepatic islet infusion as well as preceding alterations in graft function (167, 168). The use of novel noninvasive radiologic imaging techniques may be useful for this purpose and promising initial data is emerging through the use of magnetic resonance imaging (169-174) and positron emission tomography (175-178).

Another important aspect is post-transplant immune monitoring of islet transplant recipients. The limitation of the random and scattered distribution of multiple donor islet preparations into the recipient's liver renders the use of biopsies unfeasible in this patient population. Current analytical tools rely on the monitoring of panel reactive antibodies to human leukocyte antigens, mixed lymphocyte reactions *in vitro*, autoantibody to glutamic acid decarboxylase (GAD-65), autoantibody to insulin (IA-2) and lymphotoxic gene expression (179-181). The predictive value of these tests on rejection episodes and recurrence of autoimmunity is underway, but the definition of quick and reliable analytical tools that could guide clinical management is required to prevent immune-mediated loss of islet mass.

4.6 Immune interventions toward the induction of tolerance

The present and future of islet transplant, as well as that of solid organ transplantation, lies in the efficient manipulation of the immune system. In particular, there is a need in the islet transplant setting to overcome both the autoimmune process toward islet cells as well as the rejection against allogeneic tissue (91).

Current immunosuppression protocols are efficacious in prolonging islet survival by thwarting the immune system, but they lack specificity and are associated with a plethora of untoward side effects for the patients as well as for the implanted tissue—the drugs are anti-angiogenic as well as beta-cell toxic (182-184). Therefore, the drugs themselves reduce islet engraftment and may contribute to the progressive loss of function. Preventing the effects of immunosuppressive drugs appears to hinge on the efforts to restore self tolerance or to induce acceptance of transplanted allogeneic tissues. The implementation of targeted immunomodulatory approaches that selectively impair lymphocyte cytotoxicity and favor the development of regulatory phenotypes might be a viable approach toward the induction of long-term islet survival and possibly tolerance (2). Recent data from preclinical experimental models have demonstrated great promise that sustained graft survival is possible in the absence of chronic immunosuppressive drugs (185-189). Also, induction of hematopoietic chimerism in experimental systems can allow for indefinite survival of donor-specific allogeneic tissues (190, 191) and might represent a viable option for transplanted patients (192-195).

Recent clinical trials have shown some promise in preventing the progression of the autoimmune destruction of islet cell mass if implemented at onset of

autoimmune diabetes, at least in short term follow-up (196-199). Implementation of similar approaches after overt diabetes ensues might not be sufficient enough to restore normal insulin production. Potential complementary interventions may include means to enhance islet cell regeneration in the native pancreas, transplantation of autologous insulin-producing cells obtained *in vitro* from putative cell precursors as well as allogeneic islets.

5. PERSPECTIVE

The field of beta-cell replacement therapies has grown considerably during recent years. Great progress has been achieved by transplanting isolated islets in patients with T1DM with unstable diabetic control and hypoglycemic unawareness. Islet transplantation has afforded this patient population with better metabolic control, normalization of A1c, prevention of severe hypoglycemia and substantial improvement in quality of life.

The realization of beta-cell replacement therapy as a cure for T1DM may be feasible by surmounting the current shortage of islets available for transplantation and by developing safe immune interventions that restore self-tolerance and attain permanent engraftment of insulin-producing cells. The steady progress and promising results of recent clinical trials justify great optimism for the widespread application of beta-cell replacement therapy as a treatment of choice for patients with diabetes.

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