Check for updates

Islet Transplantation Alone Versus Solitary Pancreas Transplantation: an Outcome-Driven Choice?

Paola Maffi[1] · Antonio Secchi[2]

Abstract

Purpose of review In patients with type 1 diabetes with extreme glycemic variability, the restoration of pancreas endocrine function is potentially and completely achieved with islets of Langerhans (tissue derived from whole organ) or pancreas (whole organ) transplantation. The aim of our review is to report on the latest studies and to highlight the benefits and risks of the two procedures, providing clearer, more selective, evidence-based clinical indications that also consider the impact on the degenerative complications of diabetes as a potential benefit.

Recent findings Clinical experience in this field has been dynamic over the last three decades, and has been characterized by the development of more standardized protocols and a clearer definition of clinical outcome. On the contrary, the recommendations thus far are not well delineated and tend to overlap, and the past ADA position statement for pancreas transplant alone has also been applied to islet transplant alone, without differentiation.

Summary Both outcome-driven and non-outcome-driven criteria are considered in the conclusions, in an attempt to streamline indications for islet-alone or pancreas-alone transplantation.

Keywords Type 1 diabetes · Metabolic complications · Chronic complications · Pancreas transplantation · Islet transplantations · Indications for transplantation

Introduction

Type 1 diabetes mellitus (T1D) has become an important public health problem due to increased incidence globally, as well as the significant influence it has on patient survival [1], quality of life, and the development of chronic complications (cardiovascular disease, nephropathy, retinopathy, neuropathy) that frequently lead to serious disability [2•, 3, 4]. In patients

This article is part of the Topical Collection on *Immunology, Transplantation, and Regenerative Medicine*

✉ Paola Maffi
paola.maffi@hsr.it

Antonio Secchi
antonio.secchi@hsr.it

1 Diabetes Research Institute - Internal Medicine and Transplant Unit, IRCCS Scientific Institute Ospedale San Raffaele, Milan, Italy

2 Internal Medicine and Transplant Unit, Vita-Salute San Raffaele University, Milan, Italy

with diabetes who are under 30 years of age, excess mortality is mainly the result of acute complications such as diabetic ketoacidosis and hypoglycemia, whereas in older patients the main cause of death is cardiovascular disease [1]. The Diabetes Control and Complications Trial (DCCT) and its observational follow-up, the Epidemiology of Diabetes Interventions and Complications (EDIC) study, show that, compared with conventional therapy, intensive glycemic control reduces the risk not only of diabetic retinopathy, nephropathy, and neuropathy, but also of cardiovascular events, including non-fatal myocardial infarction, stroke, or death from cardiovascular disease [5]. Insulin therapy, the first treatment step for all patients with T1D, may be unsuccessful in some patients with extreme glycemic variability. Successful treatment might be found through restoration of the endocrine function of the pancreas, achieved by islet or pancreas transplantation.

Clinical experience in the field of islets of Langerhans (tissue derived from whole organs) and of whole-organ (whole pancreas) transplantation has been dynamic over the last three decades, characterized by the development of more

standardized protocols, resulting in a clearer definition of clinical outcomes and standard indications [6•].

Islet transplantation results, analyzed by the Collaborative Islet Transplant Registry (CITR), have improved since 1999, achieving the best results during the period 2007–2010 [7].

The number of solitary pancreas transplantations has remained stable over the past decade, with a stable rate of graft failure during the past 5 years [6•].

Comparative analysis of the two procedures is hampered by many issues, including donor characteristics, tissue structure (islets or vascularized whole organ), transplant approach (surgery yes or no), and immunosuppressive therapy (steroids yes or no). Furthermore, there are no statistically robust studies comparing the clinical outcomes and the risk–benefit ratios of islet versus pancreas transplant. Only a small number of transplant centers have adequate experience in both islet isolation and pancreas surgery, making it difficult to carry out prospective randomized controlled studies.

We have elected to consider papers published by the most advanced transplant centers that report their achievements in both fields, aiming to critically evaluate the results in order to better define the indications for a positive clinical outcome. The purpose of this review is to report the latest studies on islet and pancreas transplant alone in the treatment of T1D and, based on these studies, to highlight the benefits and risks of the two procedures, providing clearer, more selective, evidence-based clinical indications.

Criteria for Patient Selection

Whereas indications are clearly delineated for simultaneous pancreas-kidney (SPK) or pancreas-after-kidney (PAK) transplantation, historically considered the first choice for patients with T1D and chronic renal disease or having undergone kidney transplantation, as well as for simultaneous islet-kidney (SIK) or islet-after-kidney (IAK) transplants, the first choice in patients who cannot receive the total pancreas, indications for pancreas transplant alone (PTA) were first recommended by the American Diabetes Association in 2000. The position statement, published in the journal *Diabetes*, identified three criteria: (1) a history of frequent, acute, and severe metabolic complications (hypoglycemia, hyperglycemia, ketoacidosis) requiring medical attention; (2) clinical and emotional problems with exogenous insulin therapy that are so severe as to be incapacitating; and (3) consistent failure of insulin-based management to prevent acute complications. As part of the same recommendations, islet transplant alone (ITA) was considered an experimental approach to be used only within controlled research studies [8]. No specific standard criteria were established for each of these approaches individually, leaving it up to the transplant center to allocate patients to one or the other on the basis of their own experience. Because only a

small number of transplant centers have expertise in both PTA and ITA, clinical indications for individual patients have been guided mainly by local expertise.

Clinical Results

Islet Transplantation

In 1979, Felix Largiadèr at Zurich University first reported allogeneic pancreatic fragment infusion in patients with T1D [9]. Subsequently, only a limited series of a small number of patients underwent islet transplantation in association with kidney graft (SIK, IAK), with poor results [10]. Two important events mark a turning point in the clinical outcome of islet transplantation: in 1988, the introduction of islet isolation, as described in Ricordi's automated method [11], enabling the production of more functional tissue, together with the experiences of the Edmonton group [12], who in 2001 first transplanted islets alone (ITA) in patients with T1D, obtaining 100% insulin independence, a result that had never been achieved previously. Thereafter, islet transplant increased worldwide, and ITA became the focus of several programs.

The global picture of ITA clinical activity derives from registry data.

A CITR paper published in 2012, which includes extensive and rigorous statistical analysis comparing three different periods (1999–2002, 2003–2006, 2007–2010), reported 44% insulin independence at 3-year follow-up during the most recent period, with progressive improvement in successive periods in both ITA and SIK. Detectable secretion of C-peptide, a specific marker of tissue vitality, was reported in 83% of cases after 3 years (2007–2010) [7].

The last open-access CITR report on all islet allotransplants (ITA, IAK, SIK: 1999–2015) includes 1086 islet transplant recipients, who underwent 2150 infusions from 2619 donors [13]. Insulin independence was achieved after the second infusion in 80% of cases. Focusing on ITA, factors associated with favorable results were induction with T-cell depleting antibodies and/or TNF-alpha inhibitors, maintenance immunosuppression with a mammalian target of rapamycin (mTOR) inhibitor and calcineurin inhibitor, islet equivalents (IEQ) $\geq 325,000$, and recipient age ≥ 35 years. When these factors were present, the prevalence of insulin independence at 3 and 5 years was 50% and 40%, respectively, while C-peptide > 0.3 remained at 80% after 8 years. This is a further improvement in comparison with the data cited above.

More granular information can be obtained by analyzing the experiences of single centers to better understand clinical results. One of the most recent multicenter studies, the Clinical Islet Transplantation Consortium Protocol 07 (CIT-07), was designed as a license-enabling study in the USA [14]. The primary endpoint, eradication of severe hypoglycemia and

achievement of excellent glycemic control, was met in 87% of patients, while insulin independence at 1 year was achieved in 52.1%. Functioning islet transplants, defined as basal or stimulated C-peptide > 0.3 ng/mL, remained at 94% at 1 year. The authors highlight the elimination of severe hypoglycemic events and the restoration of hypoglycemia awareness without an increase in glycated hemoglobin (HbA1c) levels, rather than insulin independence. Scheduled immunosuppression was similar to that of previous standard protocols, with antithymocyte globulin (ATG) plus etanercept at first infusion, basiliximab in place of ATG at subsequent infusions, and Edmonton protocol immunosuppression (sirolimus and low-dose tacrolimus) for chronic maintenance. The main limitation of this study is its short follow-up (1 year). A longer follow-up of 4 years is reported in a clinical trial based on the same immunosuppression for induction, using cyclosporine and everolimus as maintenance [15]. Insulin independence was achieved in five of six patients and was maintained for 3.4 ± 0.8 years in four of them. Another single-center trial, based on Edmonton protocol immunosuppression, showed prolonged islet-function survival at 4 years, with a 57% rate of insulin independence at the last follow-up. The results of this study highlighted the correlation between good primary graft function and long-term outcome [16]. One randomized controlled trial compared the efficacy of islet transplantation and insulin therapy in patients who had severe hypoglycemia or hypoglycemia unawareness or who received kidney grafts and had poor glycemic control [17]. The primary endpoint was the modified beta score (the overall score was not zero when the stimulated C-peptide was negative) of 6 or higher after the first 6 months. Fifteen university hospitals were involved; 26 patients were assigned to islet transplantation and 24 to intensive insulin treatment. Sixteen patients receiving islet transplantation had a modified beta score of 6 or higher, versus none of the insulin-treated patients. Considering glycated hemoglobin, patients who received islet transplants had a normal value (38 mmol/mol), versus higher levels (66 mmol/mol) in the insulin group. The study design was very interesting, but it was limited by its short follow-up (6 months).

It is particularly important to emphasize that no major adverse events related to intraportal islet infusion have been observed in clinical studies. Ultrasonography combined with fluoroscopic guidance for portal puncture was associated with low risk of hemorrhage (5%), which resolved spontaneously [18]. Partial portal thrombosis, another complication related to the post-infusion period, was observed in 3.7% of cases, with spontaneous recovery after medical treatment [19].

Pancreas Transplantation

The first simultaneous pancreas-kidney transplant (SPK) was performed in 1966 at the University of Minnesota (USA) [20]. Thereafter, the number of pancreas transplantations increased progressively worldwide, characterized by different surgical techniques, immunosuppressive regimens, and finally, standardized indications [21]. In 2014, the Organ Procurement and Transplantation Network (OPTN) Board of Directors approved a uniform definition of graft failure, as follows: (1) removal of the transplanted pancreas, (2) insulin use > 0.5 U/kg/day for more than 90 consecutive days, or 3) recipient death (with a functioning graft) [22].

The University of Minnesota, the institution that pioneered pancreatic transplantation, has from the very beginning carried out the difficult task of maintaining an international registry, providing a clear picture of this procedural development over time. From December 1966 to December 2016, more than 50,000 pancreas transplants worldwide were reported to the International Pancreas Transplant Registry, with more than 30,000 performed in the USA [23]. The three leading recipient categories were SPK, PAK, and PTA.

Data from the US United Network for Organ Sharing (UNOS) updated in 2015, which included 21,328 US pancreatic transplantations performed from 1984 to 2009 with a follow-up of at least 5 years, showed SPK to be the most frequent procedure (78.5%); PTA remained stable over the previous 10 years, at 6.9% of the total, while PAK occurred at a rate of 14.6% [21]. Focusing on PTA, 90.5% of recipients had survived at 4 years. This rate is higher than that of patient survival while on the waiting list (87.3%), which has important implications, considering the indication criteria for candidates such as life-threatening metabolic complications or complete failure of insulin therapy [24]. Graft function was defined by long-term insulin independence, while graft failure was defined as the need for exogenous insulin therapy, or the occurrence of death with graft function or with partial function. Five- and 10-year PTA graft survival rates in the most recent period reached 55% and 50%, respectively. Immunosuppression trends have not changed a great deal over the past 10 years, although the use of more aggressive induction with T-cell-depleting regimens has continued to increase, and tacrolimus has evolved to become the calcineurin inhibitor of choice, with 95.5% of programs reporting its use in maintenance therapy [25] in conjunction with mycophenolate mofetil. Despite the extensive use of strong standard immunosuppressive regimens, immunological aspects seem to play an important role in graft survival, especially during the first year. Immunological graft loss of 5.6% at 1 year was reported for the period between 2011 and 2016 [23], although the method of diagnosis, treatment option, and graft rescue were not specified. Additional details were described in a biopsy-proven rejection study: pancreas rejection of any type (acute cellular rejection [ACR], antibody-mediated rejection [AMR], mixed ACR/AMR) occurred in 21% of patients undergoing different types of pancreatic transplant (SPK, PAK, PTA). AMR occurred 19% of the time after PTA, and 9% of the time after SPK. Graft failure occurred in 20% of cases of AMR,

despite a specified treatment regimen (steroids, plasmapheresis, intravenous immunoglobulin [IVIg], rituximab) [26]. Finally, surgical complications in PTA must be considered, as they increase the risk of graft loss and patient morbidity during the early post-transplant period. Technical complications in PTA occurred in 10% of recipients: graft thrombosis in 4.9% of cases, pancreatitis in 1.9%, abdominal infections in 1.2%, bleeding in 0.6%, and leakage in 0.3% [27]. Early graft failure was seen in 9.4% of cases [25].

Long-Term Benefits Concerning Complications

The results of ITA and PTA should be considered not only for their effectiveness in short- or long-term glycemic control, but also regarding the natural history of the complications of chronic diabetes. SPK and IAK long-term follow-up studies show improved clinical outcome after the normalization of glycemic control following transplantation. These patients demonstrate longer survival, fewer cardiovascular events, better transplanted kidney function, and improvements in peripheral and central neuropathy [28–33] when compared with patients with T1D who undergo kidney transplant alone.

Solitary islet or pancreas transplants have demonstrated several advantages regarding the progression of complications in chronic diabetes. As mentioned above in the UNOS data, mortality 4 years after PTA was lower than that in patients on a waiting list for this procedure (90.5% vs. 87.3%) [24], suggesting that surgery and immunosuppression are minor survival risk factors compared to brittle diabetes.

Cardiovascular risk factors, lipid profiles (total and LDL cholesterol), and blood pressure improved significantly at 5 years after PTA [34]; echocardiographic parameters, including diastolic indexes, were better at 8 years [35]. Both studies were descriptive, without a control group.

Retinopathy assessed 30 months after PTA in patients with non-proliferative retinal changes showed stabilization in 50% of cases, and 50% even showed improvement, while the control group undergoing insulin treatment demonstrated deterioration in 70% of cases [36]. Furthermore, a comparison between patients undergoing ITA and those on a waiting list revealed that central retinal velocity blood flow improved significantly 1 year after ITA [37].

Brain impairment, chronic cerebrovascular disease, and cognitive decline, all of which are characteristics of T1D, were recently studied using advanced technology, which showed normalization after a 5-year follow-up period of sustained normoglycemia in recipients of SPK [33]. After 15 months, patients who underwent ITA also showed an improvement in cerebral morphology, metabolism, and hemostatic profile using magnetic resonance imaging, nuclear magnetic resonance spectroscopy, and enzyme-linked immunosorbent assay (ELISA)/electron microscopy, along with neuropsychological evaluation. In the same study, platelet activation and pro-thrombotic factors reached near-normal values, leading to a reduced risk of hyper-coagulation when compared with patients on a waiting list for transplantation [38].

The role of ITA and PTA in nephropathy remains rather controversial, even though reversal of biopsy-proven diabetic lesions in the native kidney 10 years after PTA has been described [39]. Furthermore, a significant reduction in proteinuria some years after PTA [40] has been noted, despite calcineurin inhibitors [41]. In ITA, we have observed a decline in kidney function under tacrolimus and sirolimus only in patients suffering from mild nephropathy prior to islet transplantation [42]. In a similar setting, an abnormal glomerular filtration rate (GFR) and albuminuria at baseline have been reported as predictors of poorer kidney function after ITA [43].

Interestingly, one paper reports the outcome of a prospective one-way crossover cohort study comparing intensive insulin therapy and ITA [ref]. The median follow-up was 47 months for the insulin treatment group and 66 months for the ITA group. The authors analyzed both metabolic control and microvascular complications. Glycated hemoglobin was significantly better with ITA ($6.7\% \pm 0.2$ vs. $7.8\% \pm 0.3$ in insulin-treated participants), and participants who received ITA showed no progression of retinopathy, while insulin-treated patients had significant progression regardless of baseline grading (mild/moderate/severe non-proliferative retinopathy, proliferative retinopathy). A more rapid decline of GFR was observed in insulin-treated patients than in ITA patients already affected by micro- or overt albuminuria [44]. Similar studies do not exist for PTA.

Conclusions and Proposals

Pancreas and islet transplantation alone are presently considered potential options for the treatment of T1D when intensive insulin therapy fails and acute complications affect everyday life. Since 2000, the American Diabetes Association position statement has clearly delineated the indications for PTA, defining ITA as an experimental procedure that should be carried out only within the setting of clinical controlled trials. After the positive Edmonton experience and the establishment of several centers for islet processing and transplantation, ITA exited the experimental phase and became a feasible alternative to PTA in the clinical setting. The clinical indications for the two procedures have meanwhile expanded, with a degree of overlapping.

To choose between PTA and ITA, several items require consideration:

(1) *Biological costs in terms of organ consumption.* While PTA requires a single donor, ITA requires several

Table 1 Results and risks of pancreas (PTA) and islet (ITA) transplantation alone

	PTA	ITA
Patient survival at 5 years	91%[a]	NA
Insulin independence at 3 years	61%	44%[b]
C-peptide > 0.3 ng/mL at 3 years	NA	83%b
Technical complications	10%	3.1%[b]

NA not applicable

[a] OPTN/SRTR 2016 Annual Data Report: Pancreas [6•]

[b] Improvement in outcomes of clinical islet transplantation: 1999–2010 [7]

donors: islet processing is effective in producing transplantable islets in 50–89% of the pancreases processed. Furthermore, one to four infusions are required to achieve the desired clinical effects [45••], making the whole procedure wasteful. Organ shortage is one of the major factors limiting islet transplantation, and the need for more than one donor increases waiting-list time.
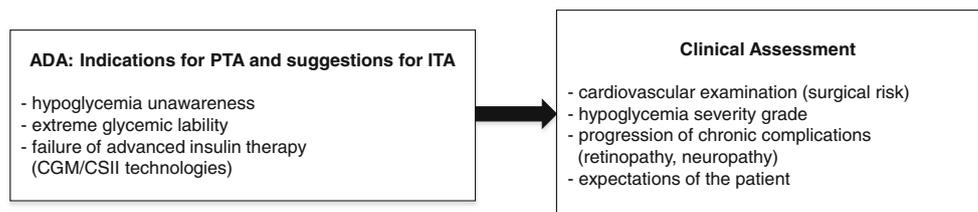
(2) *Biological costs in term of procedural complications and morbidity during follow-up.* In PTA, technical complications such as thrombosis, bleeding, and duodenal leaks can lead to re-laparotomy, and are also a risk factor for graft loss and morbidity. No major procedural complications have been registered during or following ITA infusion.

(3) *Clinical outcomes.* Insulin independence is achieved promptly upon whole pancreas transplantation, whereas it is delayed, sometimes by months or years, after islet transplantation (depending on the number and time of infusions and engraftment of

the tissue). Conversely, recovery from hypoglycemia unawareness and/or stable glycemia, with or without exogenous insulin, and graft lifespan are similar.

(4) *The baseline clinical condition of the recipient.* The occurrence of accidents related to hypoglycemia and insulin therapy, their frequency, and their incompatibility with everyday life are tolerated differently from one patient to another, depending on the severity of symptoms. The presence of cardiovascular disease that makes surgery unacceptable or risky is a crucial criterion for transplantation selection: pancreas has high surgery risk; islet has no surgery complications.

(5) *The patient's preference* and perception of risks and benefits for each procedure are essential.

In conclusion, the transplant team should consider the above points to tailor the best approach for each patient. In Table 1 we report the potential outcome/results/risks of pancreas and islet transplantation, and in Fig. 1 we propose a flowchart to define when to perform pancreas or islet transplantation. This is based on the established clinical indications for pancreas transplantation, and considers the impact on the degenerative complications of diabetes in both procedures as a potential benefit. Cardiovascular disease is not an outcome-driven criterion, and undoubtedly represents an exclusion criterion for pancreatic transplantation only. Outcome-driven criteria are the basis for the following choices: pancreatic transplantation is recommended in the presence of severe hypoglycemia, rapid progression of complications, and patient motivation, notwithstanding the clinical risk; islet transplantation is recommended in the presence of severe hypoglycemia

Fig. 1 Flowchart proposal to define when to carry out pancreas (PTA) or islet (ITA) transplantation alone

ADA: Indications for PTA and suggestions for ITA

- hypoglycemia unawareness
- extreme glycemic lability
- failure of advanced insulin therapy
  (CGM/CSII technologies)

Clinical Assessment

- cardiovascular examination (surgical risk)
- hypoglycemia severity grade
- progression of chronic complications
  (retinopathy, neuropathy)
- expectations of the patient

cardiovascular disease*	**No**	**No**	**Yes**
hypoglycemia severity grade**	**Yes**	**Yes**	**Yes/No**
fast progression of chronic complications (potential reversal with PTA)**	**Yes**	**No**	**Yes/No**
patient's willingness**	**High**	**Mild**	**Yes/No**
propensity risk**	**High**	**Mild**	**Yes/No**
Choice	**PTA**	**ITA**	**ITA**

* not outcome-driven
** outcome-driven

which is not accompanied by a rapid evolution of complications, while patient motivation remains paramount.

Compliance with Ethical Standards

Conflict of Interest   Paola Maffi and Antonio Secchi declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent   This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1. Lind M, Svensson AM, Kosiborod M, Gudbjörnsdottir S, Pivodic A, Wedel H, et al. Glycemic control and excess mortality in type 1 diabetes. N Engl J Med. 2014;371(21):1972–82. https://doi.org/10.1056/NEJMoa1408214.
2.• The Diabetes Control and Complications Trial (DCCT)/ Epidemiology of Diabetes Interventions and Complications (EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular outcomes in type 1 diabetes: the DCCT/EDIC study 30-year follow-up. Diabetes Care. 2016;39(5):686–93. https://doi.org/10.2337/dc15-1990. **This paper is important because it reports data from one of the largest and most rigorous epidemiological studies performed in a cohort of patients with type 1 diabetes, highlighting the relevance of glycemic control in cardiovascular disease, the leading cause of death for these patients.**
3. Hammes HP, Kerner W, Hofer S, Kordonouri O, Raile K, Holl RW, et al. Diabetic retinopathy in type 1 diabetes - a contemporary analysis of 8,784 patients. Diabetologia. 2011;54(8):1977–84. https://doi.org/10.1007/s00125-011-2198-1.
4. Pop-Busui R, Boulton AJ, Feldman EL, Bril V, Freeman R, Malik RA, et al. Diabetic neuropathy: a position statement by the American Diabetes Association. Diabetes Care. 2017;40(1):136–54. https://doi.org/10.2337/dc16-2042.
5. Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med. 2005;353(25):2643–53.
6.• Kandaswamy R, Stock PG, Gustafson SK, Skeans MA, Curry MA, Prentice MA, et al. OPTN/SRTR 2016 annual data report: pancreas. Am J Transplant. 2018;18(Suppl 1):114–71. https://doi.org/10.1111/ajt.14558. **This is an up-to-date account of pancreas transplantation activity in the USA, which includes all numbers of pancreas transplants centers. The knowledge of waiting list trends, donor characteristics, patient survival, graft function, and immunosuppressive protocols are benchmarks for every center with a commitment to this field**.
7. Barton FB, Rickels MR, Alejandro R, Hering BJ, Wease S, Naziruddin B, et al. Improvement in outcomes of clinical islet transplantation: 1999–2010. Diabetes Care. 2012;35(7):1436–45. https://doi.org/10.2337/dc12-0063.
8. American Diabetes Association. Pancreas transplantation for patients with type I diabetes (Position Statement). Diabetes Care. 2000;23:117.
9. Largiadèr F, Kolb E, Binswanger U. A long-term functioning human pancreatic islet allotransplant. Transplantation. 1980;29(1):76–7.
10. Alejandro R, Mintz DH, Noel J, Latif Z, Koh N, Russell E, et al. Islet cell transplantation in type I diabetes mellitus. Transplant Proc. 1987;19(1 Pt 3):2359–61.
11. Ricordi C, Lacy PE, Finke EH, Olack BJ, Scharp DW. Automated method for isolation of human pancreatic islets. Diabetes. 1988;37(4):413–20.
12. Shapiro AM, Lakey JR, Ryan EA, Korbutt GS, Toth E, Warnock GL, et al. Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. N Engl J Med. 2000;343(4):230–8.
13. Collaborative Islet Transplant Registry, 10th Annual Report, www.citregistry.org. Accessed Aug 2018.
14. Hering BJ, Clarke WR, Bridges ND, Eggerman TL, Alejandro R, Bellin MD, et al. Clinical islet transplantation consortium. Phase 3 trial of transplantation of human islets in type 1 diabetes complicated by severe hypoglycemia. Diabetes Care. 2016;39(7):1230–40. https://doi.org/10.2337/dc15-1988.
15. Bellin MD, Kandaswamy R, Parkey J, Zhang HJ, Liu B, Ihm SH, et al. Prolonged insulin independence after islet allotransplants in recipients with type 1 diabetes. Am J Transplant. 2008;8(11):2463–70. https://doi.org/10.1111/j.1600-6143.2008.02404.
16. Vantyghem MC, Kerr-Conte J, Arnalsteen L, Sergent G, Defrance F, Gmyr V, et al. Primary graft function, metabolic control, and graft survival after islet transplantation. Diabetes Care. 2009;32(8):1473–8. https://doi.org/10.2337/dc08-1685.
17. Lablanche S, Vantyghem MC, Kessler L, Wojtusciszyn A, Borot S, Thivolet C, et al.; TRIMECO trial investigators. Islet transplantation versus insulin therapy in patients with type 1 diabetes with severe hypoglycaemia or poorly controlled glycaemia after kidney transplantation (TRIMECO): a multicentre, randomised controlled trial. Lancet Diabetes Endocrinol. 2018;6(7):527–37. https://doi.org/10.1016/S2213-8587(18)30078-0.
18. Venturini M, Angeli E, Maffi P, Fiorina P, Bertuzzi F, Salvioni M, et al. Technique complications and therapeutic efficacy of percutaneous transplantation of human pancreatic islet cells in type 1 diabetes: the role of US. Radiology. 2005;234(2):617–24.
19. Kawahara T, Kin T, Kashkoush S, Gala-Lopez B, Bigam DL, Kneteman NM, et al. Portal vein thrombosis is a potentially preventable complication in clinical islet transplantation. Am J Transplant. 2011;11(12):2700–7. https://doi.org/10.1111/j.1600-6143.2011.03717.
20. Kelly WD, Lillehei RC, Merkel FK, Idezuki Y, Goetz FC. Allotransplantation of the pancreas and duodenum along with the kidney in diabetic nephropathy. Surgery. 1967;61(6):827–37.
21. Gruessner AC, Gruessner RW. Long-term outcome after pancreas transplantation: a registry analysis. Curr Opin Organ Transplant. 2016;21(4):377–85. https://doi.org/10.1097/MOT.0000000000000331.
22. Definition of pancreas graft failure OPTN policy notices: OPTN; 2015 [updated 7/2015]. https://optn.transplant.hrsa.gov/media/1572/policynotice_20150701_pancreas.pdf [Accessed 10 May 2016].
23. Gruessner AC, Gruessner RWG. Pancreas transplantation for patients with type 1 and type 2 diabetes mellitus in the United States: a registry report. Gastroenterol Clin N Am. 2018;47(2):417–41. https://doi.org/10.1016/j.gtc.2018.01.009.
24. Gruessner RW, Sutherland DE, Gruessner AC. Mortality assessment for pancreas transplants. Am J Transplant. 2004;4(12):2018–26.

25. Kandaswamy R, Stock PG, Gustafson SK, Skeans MA, Curry MA, Prentice MA, et al. OPTN/SRTR 2016 annual data report: pancreas. Am J Transplant. 2018;18(Suppl 1):114–71. https://doi.org/10.1111/ajt.1455.

26. Niederhaus SV, Leverson GE, Lorentzen DF, Robillard DJ, Sollinger HW, Pirsch JD, et al. Acute cellular and antibody-mediated rejection of the pancreas allograft: incidence, risk factors and outcomes. Am J Transplant. 2013;13(11):2945–55. https://doi.org/10.1111/ajt.12443.

27. Finger EB, Radosevich DM, Dunn TB, Chinnakotla S, Sutherland DE, Matas AJ, et al. A composite risk model for predicting technical failure in pancreas transplantation. Am J Transplant. 2013;13(7):1840–9. https://doi.org/10.1111/ajt.12269.

28. La Rocca E, Fiorina P, Di Carlo V, Astorri E, Rossetti C, Lucignani G, et al. Cardiovascular outcomes after kidney-pancreas and kidney-alone transplantation. Kidney Int. 2001;60(5):1964–71.

29. Fiorina P, Venturini M, Folli F, Losio C, Maffi P, Placidi C, et al. Natural history of kidney graft survival, hypertrophy, and vascular function in end-stage renal disease type 1 diabetic kidney-transplanted patients: beneficial impact of pancreas and successful islet cotransplantation. Diabetes Care. 2005;28(6):1303–10.

30. Fiorina P, Folli F, Bertuzzi F, Maffi P, Finzi G, Venturini M, et al. Long-term beneficial effect of islet transplantation on diabetic macro-/microangiopathy in type 1 diabetic kidney-transplanted patients. Diabetes Care. 2003;26(4):1129–36.

31. Kennedy WR, Navarro X, Goetz FC, Sutherland DE, Najaran JS. Effect of pancreatic transplantation on diabetic neuropathy. N Engl J Med. 1990;322(15):1031–7.

32. Del Carro U, Fiorina P, Amadio S, De Toni Franceschini L, Petrelli A, Menini S, et al. Evaluation of polyneuropathy markers in type 1 diabetic kidney transplant patients and effects of islet transplantation: neurophysiological and skin biopsy longitudinal analysis. Diabetes Care. 2007;30(12):3063–9.

33. Fiorina P, Vezzulli P, Bassi R, Gremizzi C, Falautano M, D'Addio F, et al. Near normalization of metabolic and functional features of the central nervous system in type 1 diabetic patients with end-stage renal disease after kidney-pancreas transplantation. Diabetes Care. 2012;35(2):367–74. https://doi.org/10.2337/dc11-1697.

34. Boggi U, Vistoli F, Amorese G, Giannarelli R, Coppelli A, Mariotti R, et al. Long-term (5 years) efficacy and safety of pancreas transplantation alone in type 1 diabetic patients. Transplantation. 2012;93(8):842–6. https://doi.org/10.1097/TP.0b013e318247a782.

35. Occhipinti M, Rondinini L, Mariotti R, Vistoli F, Baronti W, Barsotti M, et al. Amelioration of cardiac morphology and function in type 1 diabetic patients with sustained success of pancreas transplant alone. Diabetes Care. 2014;37(8):e171–2. https://doi.org/10.2337/dc14-0061.

36. Giannarelli R, Coppelli A, Sartini MS, Del Chiaro M, Vistoli F, Rizzo G, et al. Pancreas transplant alone has beneficial effects on retinopathy in type 1 diabetic patients. Diabetologia. 2006;49(12):2977–82.

37. Venturini M, Fiorina P, Maffi P, Losio C, Vergani A, Secchi A, et al. Early increase of retinal arterial and venous blood flow velocities at color Doppler imaging in brittle type 1 diabetes after islet transplant alone. Transplantation. 2006;81(9):1274–7.

38. D'Addio F, Maffi P, Vezzulli P, Vergani A, Mello A, Bassi R, et al. Islet transplantation stabilizes hemostatic abnormalities and cerebral metabolism in individuals with type 1 diabetes. Diabetes Care. 2014;37(1):267–76. https://doi.org/10.2337/dc13-1663.

39. Fioretto P, Steffes MW, Sutherland DE, Goetz FC, Mauer M. Reversal of lesions of diabetic nephropathy after pancreas transplantation. N Engl J Med. 1998;339(2):69–75.

40. Boggi U, Vistoli F, Amorese G, Giannarelli R, Coppelli A, Mariotti R, et al. Results of pancreas transplantation alone with special attention to native kidney function and proteinuria in type 1 diabetes patients. Rev Diabet Stud. 2011;8(2):259–67. https://doi.org/10.1900/RDS.2011.8.259.

41. Jenssen T, Hartmann A, Birkeland K. Long-term diabetes complications after pancreas transplantation. Curr Opin Organ Transplant. 2017;22(4):382–8. https://doi.org/10.1097/MOT.0000000000000436.

42. Maffi P, Bertuzzi F, De Taddeo F, Magistretti P, Nano R, Fiorina P, et al. Kidney function after islet transplant alone in type 1 diabetes: impact of immunosuppressive therapy on progression of diabetic nephropathy. Diabetes Care. 2007;30(5):1150–5.

43. Leitão CB, Cure P, Messinger S, Pileggi A, Lenz O, Froud T, et al. Stable renal function after islet transplantation: importance of patient selection and aggressive clinical management. Transplantation. 2009;87(5):681–8. https://doi.org/10.1097/TP.0b013e31819279a8.

44. Thompson DM, Meloche M, Ao Z, Paty B, Keown P, Shapiro RJ, et al. Reduced progression of diabetic microvascular complications with islet cell transplantation compared with intensive medical therapy. Transplantation. 2011;91(3):373–8. https://doi.org/10.1097/TP.0b013e31820437f3.

45.•• Shapiro AM, Pokrywczynska M, Ricordi C. Clinical pancreatic islet transplantation. Nat Rev Endocrinol. 2017;13(5):268–77. https://doi.org/10.1038/nrendo.2016.178. **This review outlines the key points in the development of islet transplantation, giving a clear picture of the state of the art in this field, and enables one to carefully consider the option of islet transplantation for the potential cure of type 1 diabetes**.