UPDATE ON PANCREATIC TRANSPLANTATION IN THE MANAGEMENT OF DIABETES

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ABSTRACT

Pancreas transplantation is the most effective therapeutic option that can restore insulin independence in beta-cell penic recipients with diabetes. Because of life-long immunosuppression and the initial surgical risk, pancreas transplantation is a therapeutic option only in selected patients with diabetes. Based on renal function, candidates for pancreas transplantation can be classified into three categories: uremic patients, post-uremic patients (following a successful kidney transplantation), and non-uremic patients. Uremic patients are best treated by a simultaneous kidney-pancreas transplantation. Post-uremic patients can receive a pancreas after kidney transplantation. Non-uremic patients can receive a pancreas transplant alone, if diabetes is poorly controlled resulting in hypoglycemia unawareness, and in the presence of evolving chronic complications of diabetes. Results of pancreas transplantation have improved over time and are currently non-inferior to those of renal transplantation alone in recipients without diabetes. A functioning pancreatic graft can prolong patient survival, dramatically improves quality of life of recipients, and may ameliorate the course of chronic complications of diabetes. Unfortunately, because of ageing of the donor population and lack of timely referral of potential recipients, the annual volume of pancreas transplants is declining. Considering that the results of pancreas transplantation depend on center volume, and that adequate center volume is required also for training of newer generations of transplant surgeons, centralization of pancreas transplantation activity should be considered. The recent world consensus conference on pancreas transplantation provides an independent appraisal of the impact of pancreas transplantation on modern management of diabetes as well as expert guidelines for the practice of pancreas transplantation.

INTRODUCTION

Transplantation of an immediately vascularized pancreas allograft (PTx) is currently the most effective therapy to consistently restore insulin-independence in beta-cell depleted recipients with diabetes (1-3). Islet cell transplantation may achieve the same result, especially in patients who require fewer insulin units (4-5). As compared with PTx, islet cell transplantation is associated with lower procedure-related morbidity but requires the same immunosuppression, may necessitate multiple donors, and insulin-independence, when achieved, is not often maintained long-term (1-5). However, results reported very recently from centers of excellence show, that in properly selected patients, islet cell transplantation may achieve insulin-independence rates similar to those of PTx (6).

Unfortunately, PTx is not indicated in all insulin-dependent patients with diabetes because of the initial risk associated with surgery (7) and the need for life-long immunosuppression (8). In the appropriate recipient, however, PTx prolongs survival, especially when associated with kidney transplantation (9,10), restores near-normal metabolic control (11-14), improves the course of secondary complications of diabetes (11,12,15-26) and dramatically improves quality of life (27).

PTx includes several approaches. In the most common scenario a pancreas allograft is transplanted simultaneously with a kidney in patients with insulin-dependent diabetes and end stage diabetic nephropathy (simultaneous pancreas-kidney transplantation; SPK). Grafts are typically obtained from a single deceased donor. Alternatively, a cadaver pancreas can be transplanted simultaneously with a living donor kidney (SCPLK) (28), or a segmental pancreas graft and a kidney graft can be donated from the same live donor (SLPK) (29). The pancreas can also be transplanted alone (PTA), in pre-uremic recipients, or after a successful kidney transplant (PAK), in post-uremic recipients. When the pancreas is transplanted without a kidney from the same donor, the graft is considered to be solitary because renal function cannot be used to anticipate rejection in the pancreas (so called “sentinel kidney” function) (30). In rare circumstances the pancreas is transplanted in the setting of multivisceral organ transplantation (31). This type of PTx is not considered in this review, since it is not performed in the typical recipient with diabetes to primarily reverse diabetes, but rather for technical reasons in the context of a multiorgan graft required to address specific, and rare, conditions requiring this extreme type of transplantation.

THE BURDEN OF DIABETES

Thanks to the availability of exogenous insulin therapy, Type 1 diabetes has changed from an immediately fatal disease to a chronic disease. Sub-optimal metabolic control, coupled with genetic predisposition (32-34), can lead to the development of severe secondary complications many years after the diagnosis of diabetes. These complications are associated with significant morbidity and reduce life expectancy of affected individuals. Patients with diabetes who have poor metabolic control despite intensive insulin therapy and/or who develop progressive secondary complications can benefit from PTx as near-physiologic metabolism is re-established. These complications include: retinopathy, nephropathy, neuropathy, and cardiovascular disease. Diabetic nephropathy is the leading indication to PTx, as either SPK or PAK.

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both (35). Diabetes mellitus can be classified into four types: type 1 (resulting from autoimmune destruction of beta-cells, and accounting for 5-10% of all cases), type 2 (caused by relative insulin deficiency in the setting of insulin resistance, typically associated with

obesity, and representing some 90% of the cases), gestational diabetes (first diagnosed during pregnancy), and a heterogeneous group identified as “other specific types” (35).

In nearly all countries diabetes has a high, and continuously growing, prevalence (36,37). In Western countries, these figures are mainly due to changes in life style, including diet high in saturated fats and decreased physical activity, eventually leading to obesity. Regarding type 1 diabetes, which accounts for most potential recipients of PTx, the prevalence of the disease in the United States is estimated to be 1,250,000 persons, with an annual incidence of 35,000 new cases (38).

Diabetes causes significant morbidity and increases mortality in affected individuals (35,39). The risk of heart disease and stroke is increased 3 to 5-fold, and 50-70% of patients with diabetes die of these events. Fifteen years after the onset of diabetes, diabetic retinopathy is present in the majority of patients. Eventually, 20-30% of patients with diabetes will develop severe visual impairment over the years. Reduction in the incidence of diabetic nephropathy among patients with type 1 diabetes, by approximately 10%, was overcompensated by a 20% increase in the incidence of this complication in patients with type 2 diabetes, leading to a net increase of the prevalence of diabetic nephropathy among dialyzed patients and confirming diabetic nephropathy as the leading cause of end-stage renal failure (39). Incidence of end-stage renal disease in patients with diabetes is higher compared to the patients without diabetes, with a relative risk of 6.2 in the white population and 62.0 among Native Americans. Diabetic neuropathy, in its several forms, affects up to 50% of people with diabetes. In combination with reduced blood flow, neuropathy in the feet increases up to 25-fold the chance of foot ulcers and of several fold eventual limb amputation (40).

TREATMENT GOALS IN DIABETES

There is a large amount of evidence recommending that glycated hemoglobin (HbA1c) should be maintained below 7.0% to reduce the incidence of microvascular disease (35,41). However, the effects of intensive diabetes management on the occurrence of macrovascular complications remains somewhat elusive, tending to be more evident in type 1 diabetes (42), as compared with type 2 diabetes (43,44). More stringent metabolic control (e.g., HbA1c 6.0–6.5%), when achieved without significant hypoglycemia or other adverse effects of treatment, can be preferred in patients with short disease duration, long life expectancy, and without significant cerebrovascular disease (41). On the other hand, less tight metabolic control (e.g., HbA1c 7.5–8.0%) can be accepted in patients at risk of severe hypoglycemia and/or with limited life expectancy, advanced vascular complications, or extensive comorbid conditions (41).

INDICATIONS FOR PANCREAS TRANSPLANTATION AND CANDIDATE SELECTION

PTx is performed to restore an endogenous source of servoregulated insulin production in beta-cell penic patients with diabetes. In technically successful PTx, restoration of beta-cell mass is consistently and reproducibly expected to induce insulin-independence, although at the price of significant surgical morbidity and life-long immunosuppression (2,45). In most patients with diabetes there is a clear advantage in receiving a pancreas graft, when also a kidney graft is needed to reverse end-stage renal failure. Moreover, PTx is indicated in selected patients with complicated and/or labile diabetes, when the risk of surgery and immunosuppression is surpassed by the ongoing risk of ineffective insulin therapy (2,45,46).

Based on these principles, the prototype recipient for PTx is a patient with type 1 diabetes without detectable c-peptide, poor metabolic control and/or progressive secondary complications of diabetes. However, selected patients with type 2 diabetes with high insulin needs, low to mild insulin resistance, and non- or mildly obese, may achieve insulin-independence after PTx and enjoy results similar to those of patients with type 1 diabetes (2,45,46).

Since failure of conventional, insulin-based, therapy is required to become eligible for PTx, most recipients have a 20- to 25-year history of diabetes. By this time, most recipients have developed end-stage nephropathy and also require a kidney transplant. Ideally, these patients should receive an SPK transplant because diabetic nephropathy is associated with high mortality rate, and 75% of insulin-dependent patients with diabetes do not survive longer than 5 years with dialysis (47-49). SPK improves patient survival versus either dialysis or deceased donor kidney transplantation (9,10,50).

In fragile recipients deemed not suitable for SPK, renal transplantation from a live donor is an attractive possibility either as definitive treatment or as a bridge to PAK. Actually, live donor renal transplantation may be worthily pursed also in patients otherwise eligible for SPK because of organ shortage (2,45,46). SCPLK provides an additional transplant opportunity, since it still exploits the benefits of live donation for the kidney but does not require the sequential PAK to correct the diabetes. The main disadvantages of SCPLK are the fact that the pancreas is a solitary graft, and that live renal donation cannot be programmed as it has to be performed when the deceased donor pancreas graft becomes available. To do so, three surgical teams have to work simultaneously (one for the deceased donor, one for the live donor, and one for the transplant) making organization and coordination quite complex (28). Considering that correction of uremia is key in these patients (10), but that ideal donors suitable for SPK are becoming extremely rare (51), when a deceased donor is available a kidney alone transplantation (KTA) should be considered as a valid alternative to leaving the patient with end-stage renal disease while waiting for a SPK donor, who may never become actually available. After KTA, PAK could allow correction of diabetes, thus preventing recurrence of diabetic nephropathy in the renal graft in the long-term period. Paradoxically, surgical complications associated with PAK could jeopardize renal function in the short-term period making the indication for PAK a matter of debate especially in terms of baseline renal function. Although there is no agreed cut-off of renal function to safely proceed with PAK, a stable renal function with a creatinine clearance of at least 60 ml/min/1.73 m^2, and a negative urine analysis are all considered important criteria (2,46,52).

According to the American Diabetes Association, PTA may be an option in selected patients with diabetes who have recurrent hypoglycemia unawareness, and/or have medical or psychological problems with insulin therapy (52). Normal or near-normal renal function is also required because the anticipated long-term beneficial effects of sustained insulin-independence on diabetic nephropathy may be surpassed by accelerated deterioration of renal function caused mostly by the nephrotoxic effects of immunosuppressants (22,50,53). Additional evidence shows that also patients with progressive complications (i.e., reversible nephropathy, progressive retinopathy, and severe neuropathy) may improve significantly with PTA (13,20). Although the impact of PTA on patient survival is still debated (54,55), in suitable recipients, PTA improves the course of diabetic retinopathy (18), diabetic neuropathy (13), and diabetic nephropathy (22,50,53), and reduces the level of cardiovascular risk (13,15).

Each patient eligible for PTx is, by definition, at high risk for cardiovascular disease, making cardiac and

vascular work up key in this transplant population. In recipients of solitary pancreas grafts (PAK and PTA) accurate estimate of renal function is also mandatory, as the risk of renal dysfunction/failure is reduced when the GFR is ≥ 60-70 mL/min (56). The decision to pursue a solitary PTx should hence be well balanced against the inherent risks of PTx. On the contrary, insulin-dependent patients with diabetes have in SPK their ideal treatment modality. The evaluation process in these patients should explore all possible venues to permit transplantation because continued dialysis is associated with short survival. Unfortunately, many patients are already too sick when they are first referred for transplantation and cannot be offered the chance of SPK.

Although type-2 diabetes is often characterized by obesity and peripheral insulin resistance, recent studies have demonstrated that the old paradigm is no longer generally applicable. Several studies showed improved glycemic control after pancreas transplantation in subsets of patients with type 2 diabetes, especially if body mass index is less than 35 kg/m^2 (57).

CURRENT PANCREAS TRANSPLANTATION ACTIVITY

According to the International Pancreas Transplant Registry (IPTR) and the US Organ Procurement and Transplantation Network (OPTN) approximately 51,000 PTx have been performed worldwide (> 31,000 from the United States and >20,000 from other countries) (51,56). Considering that reporting to these registries is mandatory only for US Centers, the real number of PTx performed worldwide exceeds reported registry figures.

According to IPTR data, the total number of PTx steadily increased in the United States until 2004 (peaking at a total of 1484) but has since declined substantially with fewer than 1000 procedures performed in 2014 and in 2015. The overall amount of pancreas transplants decreased slightly, from 1027 in 2018 to 1015 in 2019(56). This remains considerably higher than the nadir of 947 reported in 2015, with a slight decrease attributed to declining in PTAs (124 to 99) and PAKs (68 to 44) from 2018 to 2019. In fact, SPKs continued to increase, from 835 to 872, the highest annual number of SPKs performed in the last decade.

The reasons for the decline in PTx activity are not immediately understood. In the history of solid organ transplantation good results, such as those currently achieved by PTx, typically portend higher volumes. Decline in PTx volumes coincided with a reduction in the number of active PTx centers with only 11 Institutions performing ≥ 20 PTxs per year and most centers performing < 5 PTxs annually (51). The outcome of PTx is known to be influenced by center volume (58). Additionally, lower PTx volumes per center are expected to reduce the opportunities for training of younger generations of transplant physicians and surgeons, thus potentially worsening future outcomes of PTx and further reducing the volumes of PTx, in a vicious circle.

The reason for the current decline in PTx activity is multifactorial. Some factors are historical, such as limited referral of potential recipients (51), and incomplete procurement of pancreas grafts from otherwise suitable donors (59). Other factors, however, are newer and less correctable with educational or training programs for healthcare professionals (60). These factors include the progressive ageing of donor population (61), the increasing number of obese donors (62), and the growing proportion of cerebrovascular accidents as a cause of brain death (61). The combination of these epidemiologic factors makes the “ideal” pancreas donor (age ≤ 40 years, low BMI, death due to trauma, short stay in the intensive care unit, and hemodynamic stability without, or with low dose, vasoactive amines) extremely rare (63). These

factors, along with the duration of cold graft storage, are summarized in the Pancreas Donor Risk Index (63). This index, conceived to optimize the use of all grafts suitable for PTx, has instead promoted additional donor selection and further reduced the number of PTx (64). Although it is known that PTx can be pursued using marginal donors with good results (65,66), most centers are not willing to accept this type of donor, as their use may be associated with higher rates of early graft failure.

IMPACT OF COVID-19 PANDEMIC ON PANCREAS TRANSPLANTATION

The global coronavirus disease 2019 (COVID-19) pandemic caused by the SARS-CoV-2 virus reduced the worldwide transplant activity due to the overload of the health system and concern for patient safety. Since the first few months of the pandemic, the transplant community worked on characterizing infection, morbidity, and mortality from COVID-19 in the transplanted or waitlisted patient comparing outcomes to the general population. According to a worldwide survey, pancreas transplant activity declined shortly after the beginning of the COVID-19 pandemic because of both a reduction in patient referrals and utilization of deceased donors (67). There are limited clinical data on COVID-19 in PTx recipients, including a few case reports (68,69) and small series (70-73). As detailed in a recent review, COVID-19 in PTX recipients was mostly managed by reduction of immunosuppression with withdrawal of antimetabolites. Despite lower immunosuppression, the risk of rejection and graft loss does not appear to be clearly increased (74).

PANCREAS TRANSPLANTATION FROM DONORS AFTER CARDIAC DEATH

Shortage of suitable brain-dead donors (DBD), has forced the transplant community to explore the venue of donation after cardiac death (DCD). Based on Maastricht criteria (64) there are four categories of DCD donors. PTx is pursued in type 3 DCD donors, also known as controlled DCD donors. In this category of donors, cardiac arrest is awaited following withdrawal of ventilatory support in patients with fatal brain injuries who are not expected to progress to brain death (64). The use of this type of donors is associated with high organizational needs and may be influenced by national attitudes and regulations (65), but the results of PTx are quite encouraging making this source of grafts worth of further exploration (75-78).

In a recent systematic review and meta-analysis, Shahrestani and Co-workers identified 18 studies on PTx from DCD donors. No difference was noted in allograft survival (hazard ratio, 0.98; 95% confidence interval [95% CI], 0.74-1.31; p= 0.92), and recipient survival up to 10 years after PTx between DBD and DCD donors (hazard ratio, 1.31; 95% CI, 0.62-2.78; p= 0.47). The odds ratio for vascular thrombosis was 1.67 times higher in PTx from DCD organs (95% CI, 1.04-2.67; p= 0.006), but this difference was not evident in PTx from a subgroup of DCD who were treated with heparin (78).

GRAFT PROCUREMENT, PRESERVATION, AND TRANSPLANTATION TECHNIQUES

The history of pancreas transplantation has been shaped by developments in surgical techniques (7) and advancements in immunosuppressive regimens (79). It is now accepted that pancreas grafts are composed by the entire gland with an attached duodenal segment and that the organs are procured with minimal dissection in the donor during the heart beating period. A single arterial conduit is prepared at the back-table, usually by anastomosing the peripheral branches of a Y-shaped donor iliac graft to the cut ends of the superior mesenteric and splenic arteries (80). In rare circumstances, a segmental pancreas graft made of the body and tail of the gland, can be transplanted. This type of graft is used when

there are concerns on perfusion of the pancreatic head/duodenum to allow PTx in otherwise "difficult to transplant" recipients, such as patients with high immunization titers. A segmental pancreas graft is also used from live donors (29). Pancreas grafts are highly sensitive to ischemia-reperfusion injury (63). Despite the incidence of surgical complications not significantly increasing until 20 hours of preservation (81), most centers now prefer to maintain the period of cold storage to ≤ 12 hours (82).

At the moment, the gold standard for pancreas graft preservation is static cold storage using the University of Wisconsin solution (83). When the period of cold storage is not exceedingly long also Celsior (84) and histidine-tryptophan-ketoglutarate (85) can be accepted. The use of histidine-tryptophan-ketoglutarate has been associated with higher rates of graft pancreatitis (86). Reduction of perfusion volumes are thought to prevent these complications. IGL-1 in a newer preservation solution, but data on PTx are yet scarce (87). As with other organs, machine perfusion is being explored also for pancreas allografts. The potential of this innovative preservation strategy in PTx remains to be established (88).

Regarding transplantation techniques, it is quite surprising that none was clearly shown to be superior over the other procedures (89). Despite this, some surgical techniques have become very popular and are currently considered standard procedures for PTx. The main variations in PTx technique regard the site for venous drainage (either systemic or portal) and the site for exocrine drainage (either urinary or enteric). In enterically drained grafts other major variations are the use of a Roux-en-Y isolated loop or the creation of a direct anastomosis between the donor duodenum and the recipient small bowel (90), duodenum (91-94), or stomach (95).

The combination of systemic venous effluent and enteric exocrine drainage is currently prevalent (7) as the alleged metabolic and immunologic advantages of portal venous drainage have not been unambiguously proven (96). Bladder drainage along with the inclusion in the graft of a duodenal segment (97 PTx is not employed very frequently at the present time because of frequent urologic and metabolic complications.

The greatest innovation in surgical technique is the description of laparoscopic, robotic-assisted, PTx. The initial experience by Boggi et al (98,99) was recently duplicated at the University of Illinois at Chicago (100). This makes PTx a minimally invasive procedure and is associated with obvious advantages but has high organizational needs, and requires surgeon and team training in advanced robotic procedures.

IMMUNOSUPPRESSIVE PROTOCOLS

Current state-of-the art immunosuppression in PTx was recently reported in a review article (101) and practice recommendations were provided by the proceedings of the first world consensus conference on pancreas transplantation (WCCPTx) (102-103).

Although the immunologic outcome of PTx has improved over the years, rejection still occurs quite frequently (from 20-30% in SPK to around 40% in PTA) (104). Accordingly, the use of T-cell depleting antibody induction is still preferred in some 90% of recipients, while an anti-interleukin-2 receptor antibody alone is used in the remaining 10%. In last two decades, maintenance immunosuppression regimens have employed tacrolimus and mycophenolate in over 80% of the patients (105-106). The use of cyclosporine and/or mammalian target of rapamycin has been mostly considered in the setting of switching in case of documented side effects related to the standard regimen (107) Steroids may be withdrawn or minimized to avoid their side effects, including the risk of glucose intolerance (108-109). The recent evidence that development of donor specific antibodies occurs in PTx and is associated

with worse immunologic outcome, further compounds the field and could require the adoption of newer protocols for the treatment of antibody-mediated rejection such as a combination of anti CD20, intravenous immunoglobulins, and protease inhibitors (110). Early experiences suggest that switch from calcineurin inhibitors to belatacept, a T-cell co-stimulation blocker used to prevent acute rejection in adult renal transplant recipients, may reduce nephrotoxicity without evidence of increased risk of kidney or pancreas rejection (111,112). Belatacept may represent an important strategy for preservation of renal and pancreatic function after SPK transplantation, either as first-line or rescue therapy. A trial in primary SPK transplantation (NCT01790594), using belatacept for induction and for maintenance, in combination with mycophenolate mofetil and low dose calcineurin inhibitors, with early steroid withdrawal, was recently completed.

According to a recent review no major improvement in immunosuppressive regimens used for PTx was achieved during the last 20 years. Most PTx patients receive induction with depleting antibodies and maintenance with a combination of a calcineurin inhibitor (with tacrolimus being more prevalent than cyclosporine) plus mycophenolate and steroid maintenance. Newer drug combinations and well-designed prospective studies are needed to further improve the outcome of PTx (101).

POST-TRANSPLANT COMPLICATIONS

PTx carries the highest risk of post-transplant complications among all solid organ transplants, as a consequence of the medical complexity of recipients with diabetes and the susceptibility of pancreas allografts to develop vascular thrombosis and pancreatitis. Occurrence of post-operative complications reduces the rate of graft survival, with allograft pancreatectomy being required in some 5% of PTx recipients, but does not affect patient survival (113). Life-threatening complications still occur in approximately 3% of recipients, mostly because of development of an arterial pseudoaneurysm or an arteroenteric fistula (114).

In the long–term, malignancies as well as bacterial, viral, and fungal infections remain a significant cause of mortality and morbidity (114). Among a cohort of 360 SPK transplants, overall 5-year patient survival was 84%, but 25 recipients (6.9%) developed malignant tumors. Almost one-fourth of the cancers were skin tumors and 5 patients developed post-transplant lymphoproliferative disorders (PTLD) (106). According to the SRTR/Annual Data Report the cumulative incidence of PTLD at 4 years is 2.3% after PTA, 0.9% after SPK, and 1.1% after PAK. The higher frequency of PTLD in PTA patients is likely related to their increased immunosuppression and higher rates of acute rejection (104,116,117). The incidence of other cancers is 3- to 4-fold higher compared with the background population (115).

PATIENT AND GRAFT SURVIVAL

According to the International Pancreas Transplant Registry, 5- and 10-year graft function rates in 21,383 PTx, performed from 1984 to 2009, are 73 and 56%, respectively, for SPK; 64 and 38%, respectively, for PAK; and 53 and 36%, respectively, for PTA (1).

Cardiovascular and/or cerebrovascular events are the leading cause of recipient death either short- (<3 months post-transplant) and long-term (>1-year post-transplant) (118). In patients with type 1 diabetes, SPK has been shown in several studies to increase the observed versus expected lifespan, as compared with a kidney transplant alone (119,120). According to a large study of 13,467 patients, using data from the US Scientific Renal Transplant Registry and the US Renal Data System, the patient survival rate at 10 years post-transplant was significantly higher in recipients of a SPK than of a KTA from a deceased donor. In fact, recipients of a SPK had the greatest longevity (23.4 years), as compared with 20.9 years

for recipients of a KTA from a living donor and 12.8 years for recipients of a KTA from a deceased donor (10,121).

In recipients of PAK, evidence shows that the PTx improves long-term patient and kidney graft survival rates. Also, glomerular filtration rates are significantly higher after PAK than after KTA (122). In recipients of PTA who have brittle diabetes mellitus, the mortality rate at 4 years is lower than that in the waiting list candidates (123). Earlier reports stating a survival disadvantage for recipients of solitary pancreas transplants (PTA and PAK) compared with patients on the waiting list for a transplant now seem to be unsubstantiated (54).

Pancreas graft survival rate is based on insulin independence. In the past decade, unadjusted graft survival rates at 1 year were 89% for SPK, 86% for PAK and 82% for PTA. Equivalent figures at 5 years were 71%, 65%, and 58%, respectively (118). More recently, 10-year actual insulin independence rates have been reported to exceed 80% in SPK and 60% in PTA (12,13).

The greatest improvements are seen in the gains over time in the estimated half-life (50% function) of pancreas grafts. The estimated half-life is now 14 years for SPK, and 7 years for both PAK and PTA. Moreover, the estimated half-life has increased to 10 years in recipients of PAK or PTA with a functioning pancreas graft at 1-year post-transplant. The longest pancreas graft survival time, by category, has been 26 years (SPK), 24 years (PAK) and 23 years (PTA) (124).

The leading cause of pancreas loss is rejection (125,126). Autoimmunity is also increasingly recognized as a cause of graft failure (127,128). The diagnosis of pancreatic rejection is based on laboratory markers and imaging techniques, but core biopsy remains the final diagnostic tool. In SPK, a rise in serum creatinine can be a surrogate for pancreas rejection suspicion; however, discordant kidney and pancreas rejection have been described (129). An increase in serum amylase and lipase, although not specific, can be an initial sign of pancreatic immune-activation. Hyperglycemia occurs only in cases of severe beta-cell dysfunction or destruction, and therefore it is a late marker of rejection. Guidelines for the diagnosis of PTx rejection have been recently updated with major implementation for the identification of antibody mediated rejection (130). Pancreatic antibody mediated rejection is a combination of serological and immunohistological findings consisting of donor specific antibody detection, morphological evidence of microvascular injury, and C4d staining in interacinar capillaries. The newest Banff schema recognizes different patterns of immunoactivation, including the recurrence of autoimmune diabetes that is characterized by insulitis and/or selective beta-cell destruction. Among the different causes of graft loss, recent studies have proven that despite immunosuppression, the recurrence of autoimmune disease is not a rare event (129). Historical experience with segmental PTx in identical twins showed that, without immunosuppression, autoimmune destruction of beta cells occurs early after PTx (131). Immunosuppression prevents such recurrence in most, but not in all, patients (127).

Graft failure of any organ has a negative impact on patient survival. In recipients of SPK, kidney graft loss increases the relative risk of death by a factor of 17.6 and pancreas graft loss by a factor of 3.1. In recipients of PAK, kidney graft loss increases the relative risk of death by a factor of 4.3 and pancreas graft loss by a factor of 4.1. In recipients of PTA, pancreas graft loss increases the relative risk of death by a factor of 4.1 (132).

EFFECTS OF PANCREAS TRANSPLANTATION ON ACUTE DIABETES COMPLICATIONS

The excess mortality seen in type 1 diabetes is largely related to diabetes and its comorbidities. Acute complications are represented by hyperglycemic syndromes (most commonly ketoacidosis, less frequently the hyperosmolar syndrome) and hypoglycemia induced by exogenous insulin therapy. They contribute to 80% of all early (<10-year diabetes duration) deaths, and for a 15% of deaths thereafter. Most early acute deaths result from diabetic ketoacidosis (often at diabetes onset or after an acute illness), whereas later acute deaths tend to result from hypoglycemic episodes (133,134). Successful PTx restores a regulated endogenous insulin production and eliminates the need for exogenous insulin administration. As such, no acute diabetic complication is seen in patients with fully functioning pancreatic graft. In addition, PTx improves hypoglycemia counter-regulation, by improving catecholamine and glucagon responses to glucose lowering. These improvements are stable and long-lasting, and have been shown up to 19 years from the grafting (135). Recently, the use of beta cell replacement therapy has been discussed for patient with problematic hypoglycemia, defined as two or more episodes per year of severe hypoglycemia or as one episode associated with impaired awareness of hypoglycemia (136). In such cases, if appropriate educational and technological interventions are not sufficient to improve the condition, PTx is indicated (136). It is therefore reasonable to consider PTx in patients with type 1 diabetes who are at proven risk for serious episodes of insulin-induced hypoglycemia and who demonstrate refractoriness to conventional medical management (135,136).

EFFECTS OF PANCREAS TRANSPLANTATION ON CHRONIC DIABETES COMPLICATIONS

Chronic diabetes complications are a major burden of the disease, dramatically contributing to deterioration of quality of life and reduced survival in the population with type 1 diabetes (137). They can be broadly separated into two categories: microvascular and macrovascular. The first ones are due to damage of small vessels involving eyes, kidneys and nerves, while the others are related to damage in larger blood vessels.

Diabetic Retinopathy

Diabetic retinopathy (DR) is the most common, highly specific microvascular complication of diabetes, with prevalence strongly related to duration of diabetes and the levels of glycemic control. Numerous studies have been performed to elucidate the role of PTx on the clinical course of this complication. Initial work (138,139) found that SPK with subsequent normalization of blood glucose concentrations did not play a role in preventing or reversing retinal damage, but more recent studies support the view that PTx has beneficial effects. In a study conducted on 48 successful SPK, a careful eye examination was performed before and up to 60 months after grafting, with standardized classification of DR (19). The results showed, compared with a group of non-transplanted, matched patients with type 1 diabetes, that SPK recipients had a significantly higher rate of improvement or stabilization of the retinal lesions, depending on the severity of retinopathy at the time of transplantation. A report describing 112 patients with functioning SPK showed an improvement and/or stabilization in 73.5% patients with non-proliferative retinopathy, with an important decrease in the number or ophthalmologic procedures after a period of 4 years (140). Regarding the role of PTA, the course of DR was studied prospectively in PTA recipients and in non-transplanted patients with type 1 diabetes, with a follow-up of almost 3 years (18). The PTA and non-PTA groups consisted respectively of 33 (follow-up: 30 +/- 11 months) and 35 patients (follow-up: 28 +/- 10 months). Best corrected visual acuity, slit lamp examination, intraocular pressure measurement, ophthalmoscopy, retinal photographs, and in selected cases angiography were performed by the authors. At baseline, 9% of PTA and 6% of

non-PTA patients had no diabetic retinopathy, 24 and 29% had non-proliferative diabetic retinopathy (NPDR), whereas 67 and 66% had laser-treated and/or proliferative diabetic retinopathy (LT/PDR), respectively. No new case of diabetic retinopathy occurred in either group during follow-up. In the NPDR PTA group, 50% of patients improved by one grading, and 50% showed no change. In the LT/PDR PTA, stabilization was observed in 86% of cases, whereas worsening of retinopathy occurred in 14% of patients. In the NPDR non-PTA group, diabetic retinopathy improved in 20% of patients, remained unchanged in 10%, and worsened in the remaining 70%. In the LT/PDR non-PTA group, retinopathy did not change in 43% and deteriorated in 57% of patients. Overall, the percentage of patients with improved or stabilized diabetic retinopathy was significantly higher in the PTA group (18). Therefore, although cases of early deterioration of diabetic retinopathy have been reported after pancreas transplantation (141), current evidence indicates delay of development and/or increased rate of stabilization of this complication following functioning pancreatic graft (142,143).

Diabetic Kidney Disease

Type 1 diabetes mellitus patients present a high risk of developing renal complications. Diabetic kidney disease, or CKD attributed to diabetes, occurs in 20 – 40% of patients with diabetes and is the leading cause of end-stage renal disease (ESRD) (144). Progression to ESRD in this patient population has important prognostic implications (48,145) and proves to be resistant to most nephroprotective therapeutic measures (146). As discussed above, simultaneous pancreas-kidney transplantation (SPK) in T1D patients is associated with improved patient survival compared to solitary cadaveric renal transplantation (10,121,147,148). Regarding the survival of the grafted kidney, the SPK approach generally guarantees better results compared with the cadaveric donor kidney only transplant. In long-term results (>10 years), the kidney graft survival rate in SPK is equal or better compared to that observed with a living donor solitary renal transplantation (149). Successful long-term normoglycemia as obtained by a functioning pancreas can also prevent recurrence of diabetic glomerulopathy in the kidney graft, as shown histologically by comparing renal biopsies from SPK or PAK versus kidney transplant alone (follow-up 1 to 6 years, approximately). In addition, SPK has been reported to be associated with better creatinine levels and reduced urinary albumin excretion in SPK patients, compared to kidney alone grafted individuals (150). Along similar lines, in patients with type 1 diabetes and long-term normoglycemia after successful SPK transplantation, kidney graft ultrastructure and function were better preserved compared with LDK transplantation alone (151). Altogether, the available information indicates that pancreas transplantation plays a role in protecting the grafted kidney and preventing the recurrence of diabetic nephropathy in renal allografts.

In the case of PTA, the effects on the native kidneys are not fully established yet. Currently available immunosuppressive drugs are nephrotoxic, and this places pancreas transplantation recipients, like other solid organ recipients (152), at risk for post-transplant nephropathy (153,154). Gruessner et al. (155) showed that a serum creatinine level above 1.5 mg/dL, recipient age below 30 years and or tacrolimus levels > 12 mg/dl at 6 months were significantly associated with the development of overt renal failure after PTA. However, in another study (156) no significant deterioration of renal function was observed at 1 year after PTA in patients with glomerular filtration rate (GFR) of about 50 ml/min. Initial work from our group showed no significant change in creatinine concentration and clearance and an improvement in proteinuria at 1 year after PTA (22). More recently, we reported the results achieved in 71 PTA recipients 5 years after transplantation (13,20). In this series proteinuria improved significantly, and only one patient developed ESRD.

In the 51 patients with sustained pancreas graft function, kidney function (serum creatinine and glomerular filtration rate) decreased over time with a slower decline in recipients with pretransplant eGFR less than 90 ml/min in comparison to those with pretransplant eGFR greater than 90 ml/min; this finding is possibly due to the correction of hyperfiltration following normalization of glucose metabolism. However, another study (157) reported an accelerated decline in renal function after PTA in the patient population with lower pretransplant GFR. Important information on this issue has been provided by a study conducted with 1135 adult recipient of first PTA (55). The authors have subdivided their series of recipients into three groups, depending on the eGFR (ml/min/1.73 m^2): ≥ 90 (n: 528), 60-89 (n: 338) and < 60 (n: 269). The patients were followed up to 10 years and the outcome was ESRD, according to the need for maintenance dialysis or kidney transplantation. The results indicated that at 10 years the cumulative probability of ESRD was 21.8%, 29.9% and 52.2% in recipients with pre-transplant eGFR ≥ 90, 60-89 and < 60 ml/min/1.73 m^2, respectively (55). Overall, data available indicates the renal function before PTA as a major factor affecting post-transplantation evolution of the function of the native kidneys. The course of diabetic nephropathy after pancreas transplantation has also been characterized histologically (158-160). Fioretto et al. (161) performed protocol biopsies in patients who had received a successful PTA and found that, whereas 5 years after transplant the histologic lesions of diabetic nephropathy were unaffected, at 10 years reversal of diabetic glomerular and tubular lesions was evident. The histologic reversibility of diabetic nephropathy was previously shown in the case of transplantation of human cadaveric kidneys into recipients without diabetes (162,163) and is supported by the current favorable outcome of deceased diabetic donor kidneys (164). Of interest, a recent study has shown that mortality in PTA recipients who develop ESRD is similar to that found in type 1 diabetic patients on dialysis (165). Therefore, current evidence indicates that normoglycemia ensuing after successful pancreas transplantation prevents and may even reverse diabetic nephropathy lesions in native kidneys and kidney grafts. This has to be balanced with the potential nephrotoxic effects of immunosuppression.

Diabetic Neuropathy

Diabetic neuropathy affects approximately 50% of T1D patients and is associated with reduced survival (166,167). All types of pancreas transplantation may have beneficial effects on diabetic neuropathy (sensory, motor, and autonomic) (168-172). Navarro et al. (171) compared the course of diabetic neuropathy in 115 patients with a functioning pancreas transplantation (31 SPK, 31 PAK, 43 PTA without and 10 PTA with subsequent kidney transplantation) and 92 control patients over 10 years of follow-up. Using clinical examination, nerve conduction studies, and autonomic function tests, the authors found significant improvements in the transplanted groups (similar across the different subgroups) (171). Allen et al. demonstrated a gradual, sustained, and late improvement in nerve action potential amplitudes, consistent with axonal regeneration and partial reversal of diabetic neuropathy, in SPK recipients. Two distinct patterns of neurological recovery were analyzed: conduction velocity improved in a biphasic pattern, with a rapid initial recovery followed by subsequent stabilization. In contrast, the recovery of nerve monophasic amplitude continued to improve for up to 8 years (170). Similarly, we found a significant improvement in Michigan Neuropathy Screening Instrument scores (173), vibration perception thresholds, nerve conduction studies, and autonomic function tests in a series of PTA patients with long-term follow-up (13,20). The beneficial effects of pancreas transplantation on cardiac autonomic neuropathy were also reported by Cashion et al. (174) using 24 h heart rate variability monitoring. However, spectral

analysis of heart rate variation was performed by Boucek et al. (175), but without significant findings. Interestingly, Martinenghi et al. (172) monitored nerve conduction velocities in five patients who underwent SPK, reporting a significant improvement which was strictly dependent on pancreas graft function. Nerve regeneration is defective in patients with diabetes (166). In a case report, Beggs et al. (176) performed sequential sural nerve biopsies after PTA and found histologic evidence of nerve regeneration. Quantification of nerve fiber density in skin biopsies (177-179) or in gastric mucosal biopsies obtained during endoscopy (180) is an interesting tool to assess diabetic neuropathy. However, Boucek et al. (181,182) did not find any significant improvement in intraepidermal nerve fiber density after pancreas transplantation. In contrast, Mehra et al. used corneal confocal microscopy, a noninvasive and well validated imaging technique (183,184), and were able to find significant small nerve fiber repair within 6 months after pancreas transplantation. These latter findings have been recently confirmed (26). Lately, it has been observed that successful pancreas transplantation improved cardiovascular autonomic neuropathy (185). However, the impact of pancreas transplantation on late, serious autonomic neurological complications (gastroparesis, bladder dysfunction) is still unsettled.

Cardiovascular Disease

Patients with diabetes present an increased risk for cardiovascular morbidity and mortality, mainly due to diffuse coronary atherosclerosis and diabetic cardiomyopathy (132). After SPK, cardiovascular events remain a primary cause of morbidity and mortality (186), both in the immediate postoperative period (187) and in the long term (188). Preoperative cardiovascular assessment is mandatory to select patients who may maximally benefit from transplantation (189,190), which could also include myocardial perfusion scintigraphy (191).

In SPK recipients, improvement in macrovascular disease (including cerebral vasculopathy and morphology) and cardiac function has been generally observed. A retrospective study of cardiovascular outcomes after SPK and cadaveric kidney-alone transplantation (192) showed cardiovascular death rate (acute myocardial infarction, acute heart failure, lethal arrhythmias, acute pulmonary edema) of 7.6% in SPK, 20.0% in kidney alone and 16.1% in dialyzed patients. In the same study, SPK was associated with improved left ventricular ejection fraction, left ventricular diastolic function, blood pressure, peak filling rate to peak ejection rate ratio and endothelial dependent dilation of the brachial artery (193,194). A study by Biesenbach et al compared SPK and KTA: after 10 years from the procedure, in the SPK group the authors showed a significant lower frequency of vascular complications which included myocardial infarction (16% vs. 50%), stroke (16% vs. 40%) and amputations (16% vs. 30%). In addition, when the cardiovascular outcomes after SPK or living donor kidney-alone transplantation were compared, it was found that SPK was associated with reduced long-term cardiovascular mortality especially in a long term follow up (195). Less information is available regarding the effects of PTA on the cardiovascular system. In a single center experience with 71 consecutive PTA followed for 5 years, clinical cardiac evaluation and doppler echocardiographic examinations were performed. The authors observed that left ventricular ejection fraction increased significantly, and several parameters of diastolic function improved (13). Most of these findings were confirmed after 8 years from transplant (11). As for the effects of PTx on the peripheral arteries, the available information suggests that this type of transplantation neither aggravates nor improves peripheral vascular disease events or progression (196). However, some authors have reported that SPK is protective against atherosclerotic risk factor and progression, prothrombotic state, endothelial function and carotid intima media thickness

independent of significant changes in other risk factor (197).

FIRST WORLD CONSENSUS CONFERENCE ON PANCREAS TRANSPLANTATION

The first WCCPTx was held in Pisa (Italy) October 18-19, 2019. Based on the analysis and discussion of 597 studies, an independent jury provided 49 jury deliberations concerning the impact of pancreas transplantation on the treatment of patients with diabetes, using the Zurich-Danish model, while a group of 51 experts, from 17 countries and 5 continents, provided 110 recommendations for the practice of PTx. Consensus was reached after two online Delphi rounds with a final voting at the consensus conference on Pisa. Each recommendation received a GRADE rating (Grading of Recommendations, Assessment, Development and Evaluations) and was validated using the AGREE II instrument (Appraisal of Guidelines for Research and Evaluation II). Quality of evidence was assessed using the SIGN methodology (Scottish Intercollegiate Guidelines Network).

The WCCPTx conveys several important messages. First, both SPK and PTA can improve long-term patient survival. Second, PAK increases the risk of mortality only in the early period after transplantation, but is associated with improved life expectancy thereafter. Third, all types of PTx dramatically improve of quality of life of recipients. Fourth, depending on severity at baseline, PTX has the potential to improve the course of chronic complications of diabetes. Fifth, SPK transplantation should be performed before initiation of dialysis or shortly thereafter, as time on dialysis has negative prognostic implications for patients with diabetes. As a consequence, kidney grafts should be preferentially allocated to patients listed for an SPK transplant (102-103).

CONCLUSIONS

As shown by the WCCPTx, PTx has a high therapeutic index, when correctly indicated and performed at proficient centers. Therefore, all possible efforts should be made to make this important treatment option available in a timely manner to all suitable recipients.

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