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TRANSPLANTATION OF THE PANCREAS

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ABSTRACT

Transplantation of an immediately vascularized pancreas allograft is the only therapy that consistently restores insulin independence in beta-cell deficient patients with diabetes. However, because of the risks associated with the transplant procedure and the need for life-long immunosuppression, pancreas transplantation is a therapeutic option only for a selected group of patients. Based on renal function, pancreas transplantation can be pursued in three different recipient categories: uremic patients, post-uremic patients (after successful kidney transplantation), and non-uremic patients. Uremic patients should ideally receive a pancreas and a kidney in a single procedure (simultaneous kidney-pancreas transplantation). Post-uremic patients with good renal reserve could receive a sequential pancreas transplant (pancreas after kidney transplantation). Non-uremic recipients may be eligible for a pancreas transplant alone if they face poor metabolic control, despite optimal insulin therapy, experience hypoglycemia unawareness and/or suffer from progressive chronic complications of diabetes. The results of pancreas transplantation are now excellent and fully comparable to those of renal transplantation in non-diabetic recipients. A functioning pancreatic graft improves the quality of life of patients with diabetes, can halt, or reverse, the progression of chronic complications of diabetes, and can even prolong the life expectancy of recipients. Despite the current excellent results, the annual volume of pancreas transplantation is decreasing because of aging of the donor population and lack of timely referral of potential recipients. Considering that center volume is related to outcome, centralization of pancreas transplant activity should occur. For complete coverage of this and all related areas of Endocrinology, please visit our FREE on-line web-textbook, www.endotext.org.

INTRODUCTION

Restoration of the lost beta cell mass by pancreas transplantation (PTx) is the most effective treatment in selected patients with type 1 diabetes, able to restore insulin-independence, prolong survival, normalize most of the chronic metabolic alterations of diabetes, improve several of the secondary chronic vascular complications of the disease, and improve the quality of life (1). Different approaches may be used: simultaneous pancreas-kidney transplant (SPKT) (from a cadaveric or living donor), PTx after a successful kidney transplant (PAK) or as a PTx alone (PTA) in subjects with type 1 diabetes when the kidney function is preserved. In a few cases and in some specialized centers a pancreas is transplanted from living donors or in the setting of multi-visceral organ transplantation. In this chapter, we will discuss the indications, procedures and results of PTx, in its main approaches, as a treatment for increasing numbers of patients with diabetes mellitus.

Diabetes mellitus is a complex metabolic disease characterized by chronic hyperglycemia which leads to the development of severe secondary complications. Based on etiology, physiopathology and clinical presentation, diabetes is classified into four types: type 1 (a cellular autoimmune destruction beta cells which represents 5-10% of all cases), type 2 (resulting from impaired glucose regulation due to a combination of relative insulin deficiency and reduced insulin sensitivity, accounting for approximately 90% of cases), gestational diabetes (with onset during pregnancy), and a heterogeneous group identified as other specific types (that includes forms due to monogenic defects leading to beta-cell failure, genetic defects in insulin action, diseases of the exocrine pancreas, endocrinopathies, drugs or chemicals, infections, uncommon forms of autoimmunity, other genetic syndromes sometimes associated with diabetes) (2, 3).

The international criteria utilized to diagnose the disease are (3): a) outset with classic symptoms of hyperglycemia and a random plasma glucose value ≥ 200 mg/dl (11.1 mmol/l); b) fasting plasma glucose (FPG) value ≥ 126 mg/dl (7.0 mmol/l); c) glycated hemoglobin (HbA1c) value ≥ 6.5%; d) 2-h plasma glucose level ≥ 200 mg/dl (11.1 mmol/l) during an oral glucose tolerance test (OGTT) (3). In the absence of clear symptoms of hyperglycemia, criteria b) to d) should be confirmed by repeat testing. These criteria, however, do not apply in gestational diabetes.

There is a continuous growth of incidence, prevalence and significance of the disease (4,5). The first WHO Global report on diabetes demonstrates that the number of adults living with diabetes has almost quadrupled since 1980 to 422 million adults. The global prevalence of diabetes among adults over 18 years of age has risen from 4.7% in 1980 to 8.5% in 2014 (4). Other data, produced by The International Diabetes Federation, has estimated that there are approximately 415 million adults aged 20-79 with diabetes worldwide, including 193 million who are undiagnosed and a rising by 2040 to 642 million (5). A further 318 million adults are estimated to have impaired glucose tolerance, which puts them at high risk of developing the disease. This dramatic increase is largely associated with the rise of type 2 diabetes, due to changes in lifestyle leading to high saturated fat diet, decrease physical activity and obesity. At the same time, the incidence of type 1 diabetes, which represents the most common potential indication for transplantation, is increasing and may double the burden of disease in the youngest patients by 2020 (it is estimated that there are currently more than half a million children aged 14 and under living with type 1 diabetes) (6). The occurrence of diabetic acute complications and the development of long-term degenerative

macro and microvascular disease are associated to a high morbidity and with a 2-3-fold increase of mortality risk. The disease increases the risk of heart disease and stroke 3-5-fold, and 50-70% of people with diabetes die due to cardiovascular disease. Diabetic retinopathy occurs in approximately 2% of patients after 15 years of diabetes, and about 40-50% of patients develop severe visual impairment over the years. It represents a major cause of blindness. Despite improved therapies, diabetic nephropathy remains the leading cause of end stage renal failure, and 10-20% of people with diabetes die of kidney failure (7). In addiction, diabetic neuropathy, in one or more of its several forms, affects up to 50% of people with diabetes, and, in combination with reduced blood flow, contributes to the development of the diabetic foot, which increases up to 25-fold the chance of foot ulcers and eventual major or minor amputations.

THERAPY OF DIABETES: AN OVERVIEW

The main goals of diabetes therapy are the elimination of symptoms due to acute metabolic imbalances and the prevention of the onset of the chronic complications of the disease, to improve the quality and extend the expectancy of life of affected patients. Glycemic control remains a major focus in the management of patients, and lowering HbA1c (a major marker of glycaemia control) to <7.0%, decreases, in most cases, the onset and progression of microvascular complications (8,9). More stringent HbA1c targets (e.g. 6.0–6.5%) may be considered in patients with short disease duration, long life expectancy, no significant CVD, provided this can be achieved without significant hypoglycemia or other adverse effects of treatment (8). On the other hand, HbA1c levels of 7.5–8.0% or even slightly higher may be appropriate for patients at risk of severe hypoglycemia and/or with limited life expectancy, advanced vascular complications, or extensive comorbid conditions (8,9).

Lifestyle interventions focused, in particular, on dietary habits and physical activity are fundamental components of diabetes management (1,9). When needed (and this is the case in the vast majority of patients with type 2 diabetes) weight reduction should be pursued, in order to improve glycemic control and other cardiovascular risk factors. Even relatively modest weight loss (5–10%) contributes in this regard significantly. Dietary recommendations should be personalized and patients should be encouraged to eat healthy foods according to personal preferences and culture. Foods high in fiber, low-fat dairy products and fresh fish should be encouraged, whereas high-energy foods, including those rich in saturated fats, should be eaten seldom and in lower amounts. Physical activity should be promoted, aiming at least to 150 min/week of moderate activity including aerobic, resistance and flexibility training.

In patients with type 1 diabetes, subcutaneous insulin is the mainstay of therapy (1,10). There are several types of insulin and insulin analogs available, and various forms of administration methods, including continuous subcutaneous insulin infusion and, more recently, initial attempts with the closed-loop insulin infusion approaches have shown encouraging results (11). However, beta cell replacement therapy is the only way to achieve fully regulated normoglycemia. Insulin therapy is also needed in about 20-30% of patients with late stages of type 2 diabetes to ensure appropriate glycemic control. In this form of diabetes, however, several oral agents and non-insulin injectable drugs are available (2,8,12). Whereas a detailed description of type 2 diabetes pharmacological therapy is

beyond the purposes of this chapter, pros and cons of the available agents have been discussed in depth (8,13).

INDICATIONS FOR PANCREAS TRANSPLANTATION AND CANDIDATE SELECTION

PTx is intuitively performed with the aim of replacing the lost beta cell mass and hence restoring an endogenous source of servo regulated insulin production ensuring euglycemia. In addition, kidney transplantation may be required in patients with diabetes, due to the damage caused by diabetic nephropathy.

PTx, when technically successful, is expected to restore insulin independence in patients with diabetes, but at the expense of significant surgical morbidity and life-long immunosuppression (14,15). Therefore, PTx is indicated in selected patients with complicated diabetes, in whom the risks of surgery and immunosuppression are deemed to be lower than those of ineffective insulin therapy (14-16), which may be also influenced by genetic factors (17). Once a favourable risk/benefit balance has been established, additional benefits of PTx can also be appreciated on the side of improved quality of life (18).
Since the primary goal of PTx is restoring a critical mass of viable beta cells, the prototype recipient for this transplant is a patient with type 1 diabetes without detectable C-peptide. Recent evidence suggests that some patients with type 2 diabetes, but requiring high dose insulin and having low to mild insulin resistance (usually non- or mildly obese, may also regain insulin independence with PTx and enjoy benefits similar to those experienced by prototype recipients (14-16).

Because PTx is convenient only in patients in whom insulin-based therapies have failed, most recipients become transplant candidates after some 20-25-year history of diabetes. By this time, many of them have developed clinically relevant diabetic nephropathy and are often in end-stage renal failure. Ideally, these patients should receive a SPK. Since nephropathy is a grim prognosticator in diabetic patients (19-21), SPK is the therapy of choice for insulin-dependent patients with end-stage renal failure. Seventy-five percent of insulin-dependent patients do not survive longer than 5 years while receiving dialysis (21). However, SPK improves patient survival compared to dialysis treatment or deceased donor kidney transplant (22-24).

When a live renal donor is available, a further option is to proceed with the kidney transplant first and then correct diabetes with a PAK transplant (14-16). Actually, a live donor kidney and a deceased donor pancreas may be transplanted simultaneously but this option has high organizational needs, and has not been practiced frequently (14-16). Although sequential kidney and PAK transplantation requires two surgical operations and a dual course of induction therapy, correcting uremia is key in these patients, and the chance of a kidney transplant should not be denied simply because of the wish to pursue the “ideal” SPK path. Further, the excellent renal function provided by a live donor kidney is especially rewarding in the fragile recipient with diabetes and uremia. The rationale for PAK transplantation is to prevent the recurrence of diabetic nephropathy in the renal graft in the long-term period. PAK, however, is associated with all the typical complications of PTx which, paradoxically, may jeopardize renal function in the short-term period. 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 m2, and a negative urinanalysis are all very much welcome (14-16).

Selected patients with diabetes may also be considered for PTx alone (PTA) when native renal function is normal or “acceptable”. According to the American Diabetes Association, patients with brittle diabetes, suffering from hypoglycemia unawareness, and/or having medical or psychological problems with insulin therapy are eligible for PTA (25). Recent evidence suggests that patients having progressive diabetic complications (i.e. reversible nephropathy, progressive retinopathy, and severe neuropathy) may also significantly benefit from PTA (26,27). Whereas the impact of PTA on patient survival is still debated (28,29), in suitable recipients, PTA improves the course of diabetic retinopathy (30), diabetic neuropathy (26), and diabetic nephropathy (26,31,32), and reduces the level of cardiovascular risk (26,33). Regarding native renal function, the anticipated long-term improvement of diabetic nephropathy is thought to exceed the yet concrete risk of accelerated deterioration of renal function, which is mostly caused by the nephrotoxic effects of immunosuppressants (24,31,32).

All patients with diabetes who are potentially eligible for PTx are at high risk for cardiovascular disease, making cardiac and vascular work up key in this transplant population. In PAK and PTA recipients, great attention should be paid to the level of grafted and native renal function, respectively. In PTA, the risk of developing native kidney failure due to toxicity of immunosuppression is low with a GFR greater than 60-70 ml/min (34). The indication to proceed with a solitary PTx (either PAK or PTA) should be well balanced against the inherent risk of a complex procedure such as PTx. On the contrary, there is no good medical reason to contraindicate a SPK in patients with diabetes who have end stage renal failure, excluding the usual absolute contraindications to any type of transplant. These patients, if left on insulin and dialysis, do very poorly and die soon. Thus, the evaluation process should focus on exploring all possible venues permitting to each patient to receive his/her “life saving” SPK. Sometimes, despite all efforts, a patient with diabetes and end-stage renal failure may be felt too sick to undergo any kind of transplant (including kidney transplant alone) with a reasonable chance of success. These are simply the patients in whom the transplant evaluation was started too late in the natural course of the diseases or in whom the disease pursued a very high-grade biologic course, with virtually no chance of rescue at any time.

SURGICAL AND IMMUNOSUPPRESSIVE APPROACHES

PTX entails multiple surgical challenges, and despite decades of activity around the world, no surgical technique, and even no single surgical step, has achieved universal acceptance (35). Some techniques, however, have become prevalent and, despite not being immune from criticism, are regarded as the current standard for PTx. The typical pancreas graft is a whole pancreaticoduodenal graft. Venous effluent can be achieved either in the systemic or portal circulation, and the drainage of exocrine secretions can be created either in the gut or in the urinary bladder. Systemic venous outflow and enteric drainage are prevalent, and virtually all pancreas grafts are whole pancreaticoduodenal grafts (36,37). Regarding exocrine drainage, most groups prefer a direct anastomosis between donor duodenum and recipient small bowel, while others elect to use a Roux-en-Y intestinal limb. Newer techniques include drainage into native duodenum (38-41) and stomach (42). Drainage into

donor duodenum is possible when the pancreas is placed in the retroperitoneal space behind the right colon, as first described by Boggi et al (43), since the two duodena come to lie closely to each other, making side-to-side anastomosis immediately feasible. Beyond technical simplicity, duodenoduodenostomy allows direct access to donor duodenum for endoscopic biopsy, useful for immunologic monitoring of the pancreas graft (38). Although when allograft pancreatectomy is necessary closure of the opening on the native duodenum was described (41), and concerns remain about the safety of these maneuvers in the setting of local inflammation/sepsis.

Perhaps the greatest innovation in the surgical technique for PTx is the description of laparoscopic PTx under robotic assistance (44,45). The advantages of a minimally invasive approach would be very much welcome in the over-fragile recipients with diabetes, but this newer technique needs to be validated in large series. Since obese patients with diabetes are not only technically difficult candidates but are also at increased risk of developing various specific complications, Porubsky et al have recently reported on preemptive bariatric surgery (46). Although this possibility remains investigational, the good results achieved in uremic patients receiving a kidney alone transplant warrant further investigation in PTx (47). Recently, robotic-assisted PTx was performed at the University of Illinois at Chicago in a male patient with diabetes and a body mass index (BMI) of 41 kg/m^2, demonstrating the feasibility in severe obese patients (48).

Bladder drainage of exocrine secretions has been a cornerstone of PTx and has not been abandoned yet. Despite the description of a technique that combines bladder drainage and portal venous effluent (49), bladder drainage is typically associated with systemic venous effluent because of obvious anatomical reasons. Bladder drainage is a safe technique, since organisms cultured from graft duodenum are rarely involved in infections, and duodenal graft complications can be managed with a low risk of graft loss or patient death, often in a conservative way (50). Further, assay of urinary amylase concentration provides a sensitive marker of rejection, which is especially important in solitary PTx (51,52). Cystoscopy allows biopsy of duodenal mucosa and/or pancreas graft and may provide further clues for the diagnosis of rejection (53). Bladder drainage, however, creates a nonphysiologic condition causing unique metabolic and urologic complications. Metabolic complications are caused by urinary loss of pancreatic juice, with its high bicarbonate concentration. Although most patients compensate with increased fluid intake and bicarbonate supplementation, hyperchloremic metabolic acidosis and dehydration can occur (53). Urologic complications include hematuria (16%), duodenal segment leaks (14%), reflux pancreatitis (11%), recurrent urinary tract infections (10%), urethritis (3%), and urethral stricture/disruption (3%) (54,55). Because of these complications, conversion from bladder to enteric drainage may become necessary (52,56-62). This operation is well tolerated by most patients despite approximately one-quarter of them experiencing postoperative complications (56) which, occasionally, may lead to graft or even patient loss (52,57,63,64).

Although PTx is demonstrating fewer rejection episodes over the years, the rejection rates remain elevated (from 20-30% in SPK to around 40% in PTA) (65). This concern continues to favor the use of a T-cell depleting antibody induction in nearly 90% of recipients, whereas an anti-interleukin-2 receptor antibody is considered as a sole induction agent in only 10%. In the past 20 years maintenance immunosuppression regimens, have included tacrolimus and mycophenolate in more than 80% of cases (66,67). The switching to cyclosporine and/or

mammalian target of rapamycin has been considered in case of documented side effects related to the standard regimen (68,69). There is also a trend toward steroid withdrawal or avoidance (70,71), due to their known side effects, including the risk for glucose intolerance that would be detrimental in this patient population (72). The recent and documented impact of donor specific antibodies (DSA) on PT is advocating new protocols for the treatment of antibody-mediated rejection (AMR) such as a combination of anti CD20, intravenous immunoglobulins, and protease inhibitors (73). Preservation of renal and pancreatic function after SPK transplantation, either as first-line or rescue therapy, may be achieved with belatacept. 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. Another study (NCT02103855) investigated the switch from CNI to belatacept in PTA recipients and results will be hopefully published.

EARLY AND LATE POST-TRANSPLANT COMPLICATIONS

The fragility of recipients with diabetes, with their high burden of medical comorbidities, the propensity of the pancreas allograft to vascular thrombosis, and the need to manage the exocrine secretions of the allograft contribute to the historically high rate of early complications of PTx. These events, although not always of surgical origin, often require surgical reintervention and are hence defined as the “surgical complications” of the procedure. However, their incidence has declined over time, although some 20% of patients still require at least 1 re-laparotomy after PTx (74). Fortunately, complications requiring allograft pancreatectomy, although still representing the leading cause of early graft loss (64), now occur in less than 5% of all recipients (74). Intuitively, graft survival is reduced in the recipients who develop surgical complications, but patient survival is not affected (74). Life threatening complications may still occur in around 3% of recipients, in the form of arterial pseudoaneurysm or arteroenteric fistula (75). Duodenal graft complications are a poorly reported complication of PTx, but are an important clinical problem as they can bring to graft loss and even to patient demise. A recently published manuscript shows that in the setting of delayed duodenal graft complications, of either septic or hemorrhagic origin, timely reintervention may permit graft rescue (76). Adoption of this policy requires early recognition of duodenal graft complications and the ability to remove the entire graft duodenum with individual drainage of the pancreatic duct in the bowel. Centers without these skills, or with insufficient experience, should send patients thought to have duodenal graft complications to qualified Institutions for attempted patient and graft rescue.

Over the past decade, patient and graft survival rates in PTx have significantly improved (see below). Nonetheless, malignancies and infections remain a significant cause of mortality and morbidity (77). In a recent study (78), the authors retrospectively analysed the incidence of a neoplasm among 360 diabetic subjects who consecutively underwent SPKT in their institution. The overall 5-year patient survival was 84%. Twenty-five patients developed malignant tumors. Almost one-fourth of the cancers were represented by skin tumors (3 squamous cell and 4 basal cell carcinomas) and PTLD was diagnosed in 5 recipients. The cumulative incidence of PTLD from SRTR/Annual Data Report 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 (65,79,80). The incidence of other cancers is 3- to 4-fold higher compared with the background

population (78).

PATIENT AND GRAFT SURVIVAL

More than 50,000 PTx have been performed worldwide (> 29,000 from the United States and >19,000 from other countries), and patient survival rates have improved significantly over time in all categories of recipients (81). According to the International Pancreas Transplant Registry, unadjusted patient survival rates are >96% at 1 year post-transplant and >80% at 5 years. In some single center experiences, high actual patient survival at 10 years has been reported in both SPK and PTA (26,82). Cardiovascular and/or cerebrovascular problems and infections remain the leading causes of early (<3 months post-transplant) and late (>1-year post-transplant) death after PTx (83). In patients with type 1 diabetes (T1DM), an SPK has been shown in several studies to increase the observed versus expected lifespan, as compared with a kidney transplant alone (84,85). According to a large study of 13,467 patients that used 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 SPK than of kidney transplant from a deceased donor. In fact, recipients of SPK had the greatest longevity (23.4 years), as compared with 20.9 years for recipients of a kidney transplant from a living donor and 12.8 years for recipients of a kidney transplant from a deceased donor (23,86).

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 in the kidney graft of recipients of PAK than in recipients of kidney transplants alone (87) In recipients of PTA who have brittle diabetes mellitus, the mortality rate at 4 years is lower than that in the waiting list candidates (28). Earlier reports stating a survival disadvantage for recipients of solitary PTx (PTA and PAK) compared with patients on the waiting list for a transplant now seem to be unsubstantiated (28,29).

Pancreas graft survival rate is based on insulin independence. In the past decade, unadjusted graft survival rates at 1 year were 89% (SPK), 86% (PAK) and 82% (PTA). The figures at 5 years were 71% (SPK), 65% (PAK) and 58% (PTA) (83). More recently, (26,82) 10-year actual insulin independence rates have been reported to be >80% in SPK and >60% in PTA.

The most impressive 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 (SPK), 7 years (PAK) and 7 years (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).

The leading cause of pancreas loss is rejection (88,89). Autoimmunity is also increasingly recognized as a cause of beta cell failure (90-93). The diagnosis of pancreatic rejection is based on laboratory markers and imaging techniques with the understanding that the core biopsy remains the diagnostic gold standard tool. In SPK, a rise in serum creatinine can be a surrogate for pancreas rejection suspicion; however, dyssynchronous kidney and pancreas rejection have been described (94). 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 (72). Guidelines for the diagnosis of PTx rejection have been recently updated with major implementation for the identification of AMR (95). Pancreatic AMR is a combination of serological and immunohistological findings consisting of DSA 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 (91,95). Early experience with segmental PTx in identical twins without immunosuppression showed that autoimmune destruction of beta cells occurs early after PTx (96-99).

Immunosuppression prevents such recurrence in most, but not in all, patients (90-94). Differently from the more frequent alloimmune reaction, producing graft rejection, recurrence of autoimmunity is characterized by isolated hyperglycemia without functional impairment of the exocrine pancreas or renal allograft function. In these patients, islet cell autoantibodies against GAD, IA-2, and ZnT8 antigens have usually persisted, have increased, or have reappeared after PTx (90,91,93), and are accompanied by the presence of circulating autoreactive CD4 or CD8 T-cells (100). Biopsy shows insulitis and beta-cell loss and lack features typically associated with graft rejection (90,91). Although the presence of autoantibodies does not contraindicate PTx, and most PTx recipients have detectable autoantibodies at the time of PTx, autoantibody conversion increases the risk of developing recurrent type 1 diabetes (90,91). In the presence of immunosuppression, rise of autoantibodies precedes hyperglycemia by several years (90,91).

Treatment options are nonspecific and include more sophisticated immunosuppressive therapies to target T-cells, B-cells, and autoantibodies. Plasmapheresis may be used to lower islet cell antibodies although, as shown in patients with newly diagnosed type 1 diabetes, the level of GAD autoantibodies may not be affected (90,91). Polyoma virus (BK) can induce a severe nephropathy (BKVN), an important cause of kidney graft loss following SPK and PAK. Routine screening for BK viremia and early treatment in case of positivity may protect from BKVN development. Recent data have shown that calcineurin inhibitor and mycophenolate reduction and introduction of leflunomide may be crucial for stopping BK reactivation (101).

Graft failure of any organ has a negative impact on 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 (81).

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 modified Maastricht criteria (102) 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 non-survivable brain injuries who are not expected to progress to brain death (102). The use of this type of donors is associated with high organizational needs and may be influenced by national attitudes and regulations (103), but the results of PTx are quite encouraging making this source of grafts worth of further exploration (104-107).

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 (107).

In a recent study, Kopp et al described the results of 104 PTx, 21 of which from DCD donors: postoperative bleeding and kidney delayed graft function was observed more frequently in recipients from DCD (p=0.006). However, DCD pancreata had a lower incidence of thrombosis in contrast to previous studies (108,109). The authors concluded that results of PTX from DCD donors with a relatively low pancreas donor risk index (PDRI) were similar to DBD donors. Donor age was the only donor related risk factor associated with pancreas graft survival (HR 1.06, p=0.037) (110).

Recently, a European expert group provided recommendations on utilization of DCD donors for pancreas and islet transplantation specifying a limit of 30 minutes for warm ischemia time. Maastricht Class III and IV DCD donors were considered reasonably suitable for vascularized PTx, excluding preferably donor aged >50 years and with a BMI>30 kg/m^2 (111).

EFFECTS OF PANCREAS TRANSPLANTATION ON GLUCOSE AND LIPID PARAMETERS

Successful PTx restores endogenous, regulated insulin secretion, thus leading to normal glucose and HbA1c levels (112). Insulin release from the transplanted pancreas can be normally elicited by glucose and non-glucose oral stimuli (113) and shows well maintained first- and second-phase secretion in response to intravenous glucose (114). Physiologically, insulin secretion is characterized by low-frequency ultradian and high-frequency oscillations. It is not clear if denervation of the pancreas graft affects this pulsatility, with some (115) but not all (116) authors reporting changes in frequency and amplitude of cycles. Fasting insulin concentrations are 2-fold to 3-fold higher than normal when PTx is performed with systemic venous drainage, due to a delay in first-pass hepatic extraction (117). C-peptide levels do not show this pattern, since this peptide, normally secreted in equimolar proportion with insulin, has a negligible liver extraction (118). In contrast, no significant change in insulin levels are observed with portal vein delivery, compared with normal subjects. The metabolic implications of systemic vs venous insulin delivery on glucose homeostasis have been investigated in a few studies and, overall, the available evidence shows that there are no major differences in most glucose metabolism parameters, including those related to insulin sensitivity and beta-cell function, between the two procedures (119,120).

SPK transplant improves lipid profile and lowers fasting triglycerides; in addition, increased high-density lipoprotein (HDL) cholesterol, increased low-density lipoprotein (LDL) particle size, increased lipoprotein lipase activity, and improved postprandial lipemia have been usually observed, compared with kidney transplant alone (121-123). The effects of PTA on lipid concentrations are also being discussed. Triglycerides were found to be higher at 1 year posttransplant in a study using predominantly cyclosporine-based immunosuppression and systemic insulin drainage (124). However, a nonsignificant 14% and 8% decrease of LDL-cholesterol 1 and 2 years after PTA has been reported in a small group of patients with systemic venous drainage (125). In more recent studies using tacrolimus-mycophenolate mofetil-based immunosuppression and portal insulin drainage, total and LDL-cholesterol improved, and triglycerides were unchanged, without any major modification of the anti-dyslipidemic therapy (26,33).

The relative effects of systemic and portal insulin drainage on lipid metabolism remain controversial. It was initially reported that cholesteryl ester transfer levels were significantly higher in patients receiving systemic venous drainage compared with those receiving portal drainage (126). In another study, it was observed that portal drainage resulted in normalization of insulin mediated suppression of plasma free fatty acid (FFA) levels compared with systemic drainage (127); nevertheless, both procedures were associated with a similar mild elevation of circulating very low density lipoprotein (VLDL) particles that resulted from an approximately 50% reduction in VLDL clearance compared with healthy control subjects (127). A randomized, prospective study compared the metabolic effects of systemic and portal insulin delivery by euglycemic hyperinsulinemic clamp (119). Basal and under-clamp FFA levels were similar and, in addition, no significant difference in cholesterol and low-density lipoprotein levels was shown; high-density lipoprotein levels and triglycerides during fasting and under clamp were significantly higher in the systemic venous drainage group (119). However, when the effects of SPK were recently assessed in 147 and 45 recipients with systemic and portal vein delivery, respectively, no difference in lipid parameters was found in the 2 groups (128).

EFFECTS OF PANCREAS TRANSPLANTATION ON DIABETES MICROVASCULAR AND MACROVASCULAR COMPLICATIONS

Diabetic retinopathy (DR) is the most common microvascular complication of diabetes, and several studies have been performed to assess the role of PTx on the course of this complication 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. Earlier studies denied a role of insulin-independence achieved by SPK in preventing or reversing retinal damage (129-130). More recent studies, however, showed that sustained normalization of blood glucose concentrations results in beneficial effects on the evolution of diabetic retinopathy. In a study from Giannarelli and co-workers, a careful eye examination was performed before and up to 60 months following PTx, with standardized classification of DR (30). In this study when the evolution of DR was compared between SPK recipients and a group of non-transplanted, matched patients with type 1 diabetes, PTx was associated with a significantly higher rate of improvement or stabilization of retinal lesions, depending on baseline severity of DR. In a more recent study form De Sá

and co-workers on 112 patients with functioning SPK the authors reported that non-proliferative DR improved and/or stabilized in 73.5% of the recipients, with a relevant decrease in the number of ophthalmologic procedures over a period of 4 years (131).
The impact of PTA on the course of DR was assessed prospectively in PTA recipients and in non-transplanted patients with type 1 diabetes during a period of approximately 3 years (30). In this study, there were 33 PTA recipients (follow-up: 30±11 months) and 35 non-transplanted patients with diabetes (follow-up: 28±10 months). The following parameters were assessed: best corrected visual acuity, slit lamp examination, intraocular pressure measurement, ophthalmoscopy, retinal photographs, and in selected cases angiography. At baseline, no signs of DR could be detected in 9% of PTA and in 6% of non-PTA patients. Non-proliferative diabetic retinopathy (NPDR), was identified in 24% and 29% of the patients, respectively. Equivalent figures for laser-treated and/or proliferative diabetic retinopathy (LT/PDR) were 67% and 66%, respectively. During the follow-up, there were no cases of newly diagnosed DR in either group. NPDR improved by one grade in 50% of the patients after PTA and showed no change in the remaining patients. In the control group NPDR improved in 20% of the patients, remained stable in 10% and worsened in 70%. LT/PDR stabilized in 86% of the patients after PTA whereas deterioration was recorded in 14%. Equivalent figures in the control group were 43% and 57%, respectively. When these results are considered all together, PTA was associated with improved evolution of DR as compared to the control group consisting of patients remaining under intensive insulin treatment (30).

Patients with type 1 diabetes mellitus 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) (132). Progression to ESRD in this patient population has important prognostic implications (20,133) and proves to be resistant to most nephroprotective therapeutic measures (134). As discussed above, SPK in patients with type 1 diabetes is associated with improved patient survival compared to solitary cadaveric renal transplantation (23,85,135,136). 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 (137). 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 have been reported to be associated with better creatinine levels and reduced urinary albumin excretion in SPK patients, compared to kidney alone grafted individuals (138). Altogether, the available information indicates that PTx 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 PTx recipients, like other solid organ recipients (139), at risk for post-transplant nephropathy (140,141). Gruessner et al. (142) 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 (143) 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 (31). More recently, we reported the results achieved in 71 PTA recipients 5 years after transplantation (26,27). 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 pre-transplant eGFR less than 90 ml/min in comparison to those with pre-transplant eGFR greater than 90 ml/min; this finding is possibly due to the correction of hyperfiltration following normalization of glucose metabolism. However, another study (144) reported an accelerated decline in renal function after PTA in the patient population with lower pre-transplant GFR. Important information on this issue has been provided by a study conducted with 1135 adult recipient of first PTA (34). 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 (34). 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 PTx has also been characterized histologically (145-147). Fioretto et al. (28,148) 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 nondiabetic recipients (149,150) and is supported by the current favorable outcome of deceased diabetic donor kidneys (151). Of interest, a recent study has shown that mortality in PTA recipients who develop ESRD is similar to that found in patients with type 1 diabetic on dialysis (152).

Diabetic neuropathy affects approximately 50% of patients with type 1 diabetes and is associated with reduced survival (153,154). All types of PTx may have beneficial effects on diabetic neuropathy (sensory, motor, and autonomic) (155-159). Navarro et al. (158) compared the course of diabetic neuropathy in 115 patients with a functioning PTx (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) (158). 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 analysed: 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 (157). Similarly, we found a significant improvement in Michigan Neuropathy Screening Instrument scores (160), vibration perception thresholds, nerve conduction studies, and autonomic function tests in a series of PTA patients with long-term follow-up (26, 27). The beneficial effects of PTx on cardiac autonomic neuropathy were also reported by Cashion et al. (161) using 24 h heart rate variability monitoring. However, spectral analysis of heart rate variation

was performed by Boucek et al. (162), but without significant findings. Interestingly, Martinenghi et al. (159) 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 (153). In a case report, Beggs et al. (163) performed sequential sural nerve biopsies after PTA and found histologic evidence of nerve regeneration. Quantification of nerve fiber density in skin biopsies (164-166) or in gastric mucosal biopsies obtained during endoscopy (167) is an interesting tool to assess diabetic neuropathy. However, Boucek et al. (168,169) did not find any significant improvement in intraepidermal nerve fiber density after PTx. In contrast, Mehra et al. used corneal confocal microscopy, a non-invasive and well validated imaging technique (170,171), and were able to find significant small nerve fiber repair within 6 months after PTx. These latter findings have been recently confirmed. However, the impact of PTx on late, serious autonomic neurological complications (gastroparesis, bladder dysfunction) are still unsettled.

Patients with diabetes are at high cardiovascular risk, mostly because of diffuse coronary atherosclerosis and diabetic cardiomyopathy (81). Probably because SPK is performed late in the natural history of the disease, when irreversible renal damage has already occurred, cardiovascular events continue to occur in SPK recipients causing significant morbidity and mortality (172). This risk obviously exists in the immediate post-PTx period (173) and is not eliminated in the long term (174). As a consequence pre-transplant cardiovascular assessment is key not only to select suitable recipients but also to identify the patients who are expected to enjoy the highest degree of benefit from SPK (175,176). Pre-transplant cardiovascular workup may also include myocardial perfusion scintigraphy (177) and, in selected patients, invasive cardiovascular tests. In this recipient category improvement in cardiovascular risk and cardiac function has been generally observed. In a retrospective study, La Rocca et al. demonstrated lower rates of death caused by cardiovascular events in SPK patients (7.6%) as compared with recipients of solitary kidney transplantation from deceased donors (20.0%) (178). SPK was also associated with improved cardiac function as demonstrated by evidence of 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 (179, 180). An additional study from Biesenbach et al showed that 10 years after SPK or solitary kidney transplantation the rate of vascular complications was lower in the former group of recipients. Namely, the frequency of myocardial infarction was 16% vs 50%, the rate of stroke was 16% vs 40%, and the need for amputations was 16% vs 30%. In this study the authors also investigated the impact of a kidney transplantation from living donors on the risk of cardiovascular complications and showed that even with the use of a live donor the cardiovascular outcome after SPK was superior when compared to that observed following solitary kidney transplantation especially in a long term follow up (181). The effects of PTA on the cardiovascular system have been studied less extensively. A single center study reporting on 71 consecutive PTA followed for at least 5 years, showed significant improvement of the left ventricular ejection fraction as well as of several parameters of diastolic function (26).

Regarding the effects of PTx on peripheral arteries, available data suggest that this type of transplantation neither aggravates nor improves peripheral vascular disease events or progression (182). There is however some evidence that SPH could prevent the aggravation of atherosclerotic risk factors (183).

CONCLUSIONS

PTx is the only therapeutic venue that can restore insulin independence in beta cell deficient recipients with diabetes. Because of the need for life-long immunosuppression and the initial surgical risk, PTx is a therapeutic option only in a sub-group of patients with diabetes. The number of PTx performed annually is declining because of either aging of deceased donor population and yet incomplete awareness of the full therapeutic potential of this type of transplantation, resulting in limited patient referral. Considering that PTx outcome depends on center volume, and that adequate center volume is required also for training of newer generations of transplant physicians and surgeons, centralization of PTx activity should occur.

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