Kidney-Pancreas Transplantation

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31.1 Introduction

Beta-cell-penic diabetic patients require insulin therapy, appropriate dietary intervention, and regular exercise in order to achieve tight metabolic control and reduce the incidence and the severity of chronic complications of diabetes [1]. Most patients do acceptably well under this therapeutic regimen, but intensive insulin treatment does not completely eliminate chronic complications and carries the significant risk of hypoglycaemia [2].

Depending on their severity, diabetic complications may be partially or totally reversed by pancreas transplantation, but their development carries negative prognostic implications. Diabetic nephropathy, in particular, decreases life expectancy [3–11]. Proteinuria alone produces a 15-fold increase in the risk of heart disease, compared with non-proteinuric diabetic patients, and a 40-fold increase, compared with the general population [4, 6]. When requiring dialysis, 75 % of insulin-dependent diabetic patients do not survive longer than 5 years [12–20].

Simultaneous pancreas-kidney (SPK) transplantation is currently considered the preferred therapeutic option in beta-cell-penic diabetic patients with end-stage renal

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failure. Some patients, however, may initially receive a renal transplant, often from a live donor, and subsequently become candidates for a pancreas after kidney transplantation.

31.2 Indications

Kidney-pancreas transplantation is indicated in diabetic patients with imminent or established end-stage renal disease [21]. The procedure renders patients free of renal failure and provides a physiological means of achieving normoglycaemia, which associates with increased life expectancy, elimination of the acute complications commonly experienced by patients with diabetes, and beneficial impact on long-term vascular complications [22, 23].

31.2.1 Diabetes and Its Burden

Diabetes is one of the most common chronic diseases in nearly all countries and continues to increase in number and significance [24, 25]. The International Diabetes Federation reports that the current prevalence of diabetes among adults aged 20–79 years in the world is of around 8 %, corresponding to more than 380 million people, increasing to 592 million people in 2035, in accordance with recent estimations [25]. The disease can be diagnosed by the use of the following criteria [24]: (a) presence of classic symptoms of hyperglycaemia or hyperglycaemic crisis 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), with fasting defined as no caloric intake for at least 8 h before the test; (c) glycated haemoglobin (HbA1c) value ≥6.5 % [provided the test is performed in a laboratory using a method that is National Glycohemoglobin Standardization Program (NGSP) certified and standardized to the Diabetes Control and Complications Trial (DCCT) assay]; (d) 2-h plasma glucose level ≥200 mg/dl (11.1 mmol/l) during an oral glucose tolerance test (OGTT), using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water. In the absence of clear symptoms of hyperglycaemia, criteria (b) to (d) should be confirmed by repeat testing. In addition, three categories of increased risk for diabetes have been identified: impaired fasting glycaemia (IFG) for FPG values of 100–125 mg/dl (5.6–6.9 mmol/l); impaired glucose tolerance (IGT), for 2-h plasma glucose on the 75-g OGTT between 140 and 199 mg/dl (7.8–11.0 mmol/l); and the situation when HbA1c value is 5.7–6.4 % [24]. For all these three conditions, risk is continuous, extending below the lower limit of the range and becoming greater at higher ends of the range [24]. On the basis of aetiology and clinical presentation, diabetes is classified into four types: type 1 (caused by autoimmune destruction of the insulin-producing beta-cells in the pancreas and representing 5–10 % of all cases), type 2 (characterized by relative insulin deficiency and insulin resistance, very often associated with obesity, and accounting for approximately 90 % of cases),

gestational diabetes (with onset or first recognition during pregnancy), and an heterogenous 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, and other genetic syndromes sometimes associated with diabetes [24].

Diabetes is associated with high morbidity and increased mortality [24, 25]. The disease enhances the risk of heart disease and stroke two- to fourfold, and 50–70 % of people with diabetes die of these events. Diabetic retinopathy is a major cause of blindness that occurs in approximately 2 % of patients after 15 years of diabetes; moreover, about 40–50 % of patients develop severe visual impairment over the years. Despite improved therapies, diabetes remains the leading cause of kidney failure, and 10–20 % of people with diabetes die of kidney failure (see also below). 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, neuropathy in the feet increases up to 25-fold the chance of foot ulcers and eventual limb amputation severalfold. Finally, close to four million deaths in the 20–79 age group may be attributable to diabetes in 2010, and the proportion of deaths due to diabetes in people under 60 years of age was close to 50 % in 2013 [25].

31.2.2 The Role of Kidney-Pancreas Transplantation

It is accepted that 20–40 % of diabetic patients develop diabetic nephropathy over a period of 25 years from the diagnosis of disease, and 5–15 % progress to ESRD [24, 25]. Persistent albuminuria in the interval of 30–299 mg/24 h is considered an early stage of diabetic nephropathy in type 1 diabetes and a marker for development of nephropathy in type 2 diabetes [24]. Although evidence has been provided to show spontaneous remission of albuminuria in this category (up to 40 %) or stabilization without progressing to more elevated levels of albuminuria (≥300 mg/24 h) over 5–10 years of follow-up (30–40 %), the remaining patients will tend to move to the more significant levels of ≥300 mg/24 h and will be likely to progress to ESRD [24]. These patients will ultimately require life-sustaining, long-term renal replacement therapy, either in the form of dialysis or kidney transplantation. In the presence of type 1 diabetes, and in selected cases of type 2 diabetes, patients could benefit of a kidney-pancreas transplantation. The first kidney and pancreas transplant was performed in 1966 by William Kelly and Richard Lillehei at the University of Minnesota, USA [26]. Since then, more than 40,000 pancreas transplants have been performed worldwide [27]. Of them, >80 % have been done in patients with kidney failure who therefore have undergone a simultaneous pancreas-kidney (SPK) transplantation. In approximately 10 % of cases, a kidney transplant has been performed first, followed by a pancreas after kidney transplant (PAK) because of poor glycaemic control or progression of chronic vascular diabetic complications, including the possible development of diabetic nephropathy in the transplanted kidney. In many cases (75 % in 2012), recipients of a PAK have first undergone a living donor

kidney transplant [27]. The remaining 8–10 % of pancreas transplants (pancreas transplant alone, PTA) have been done in diabetic patients with preserved renal function, but experiencing extreme diabetes instability and/or progressive vascular diabetes complications [28, 29]. In PTA, patients may develop end-stage renal disease due to the nephrotoxic effects of immunosuppressive drugs (calcineurin inhibitor in particular), which, in turn, may lead to a subsequent kidney transplantation (around 6 % at 5 years) [29]. Renal function before PTA is a strong predictor of end-stage renal disease after PTA, with cumulative risk at 10 years increasing from 21.8 % with pre-PTA estimated glomerular filtration rate (eGFR) of ≥90 ml/min/1.73 m^2 to 52.2 % with eGFR <60 ml/min/1.73 m^2 [30]. In the SPK and PTA categories, 1- and 5-year patient survival is of around 95 % and >80 %, respectively, and the corresponding kidney graft survivals are of approximately 95 % (1 year) and 80 % (5 years) [27]. The current 1- and 5-year survival rates for the pancreatic graft are 89 and 71 % in SPK, 86 and 65 % in PAK, and 82 and 58 % in PTA, with a clear trend to further improvements [27, 28, 31–33].

31.2.3 Criteria for Kidney-Pancreas Transplantation

Since kidney-pancreas transplantation has beneficial effects on life expectancy, course of microvascular and macrovascular diabetes complications, and quality of life [27, 28, 31–33], the procedure is indicated in type 1 diabetic patients with end-stage renal disease (on dialysis or in the pre-emptive stage), in whom the risks of surgery and immunosuppression are deemed acceptable and lower than those of dialysis therapy and scarcely effective insulin therapy. Selected type 2 diabetic patients (not obese, with progressive vascular diabetic complications) can also be considered [27–29, 34]. Indications and admission criteria for kidney-pancreas transplantation in our centre, which are based on available evidence [27–29, 31–34], are as follows: end-stage renal disease (on haemodialysis or peritoneal dialysis) and type 1 diabetes [selected type 2 diabetic patients (not obese and with chronic diabetes vascular complications) may also be considered]; chronic renal failure (before dialysis – pre-emptive – with measured LOW glomerular filtration rate) and type 1 diabetes [selected type 2 diabetic patients (not obese and with chronic diabetes vascular complications) may also be considered]; severe nephrotic syndrome and type 1 diabetes [selected type 2 diabetic patients (not obese and with chronic diabetes vascular complications) may also be considered]; acceptable surgical and immunosuppressive therapy risks; appropriate psychosocial attitudes; age <60 years; the absence of additional exclusion criteria. The latter that may be permanent or temporary include HIV positivity [with the exception of admission in specific protocols [35]], neoplasms (also depending on tumour type and biology, activity, clinical and pathologic stage, duration of disease-free period), infections, severe heart diseases and/or polidistrectual atherosclerosis, severe chronic respiratory failure, liver failure, uncorrectable urinary tract abnormalities, bilateral iliac vein thrombosis, chronic coagulopathies, psychiatric diseases, mental retardation, drug addiction (including chronic ethylism), and severe obesity.

31.3 Timing

Diabetic patients do poorly under dialysis. As a consequence, the earlier the transplant, the better the result.

An analysis on 6,496 patients showed that pre-emptive SPK ($n=1,466$) was associated with an adjusted 17 % reduction (HR = 0.83; 95 % CI, 0.69–0.98; $p=0.042$) in the rate of kidney allograft failure compared to non-pre-emptive SPK. The benefit of pre-emptive SPK persisted with the composite outcome of mortality from any cause or kidney allograft loss, irrespective of the modality used to deliver chronic dialysis [36].

Becker et al. reported a registry analysis on 11,825 type I diabetic patients who underwent a first kidney transplantation alone or SPK transplantation. Most patients ($n=10,118$) had non-pre-emptive transplantation (living donor kidney = 2,438; deceased donor kidney = 3,375; deceased donor SPK = 4,305). The remaining 1,707 patients were transplanted pre-emptively (living donor kidney = 714; deceased donor kidney = 169; deceased donor SPK = 824). Pre-emptive SPK was associated with a lower risk for graft loss (adjusted risk ratio [RR] graft failure, 0.79; $p=0.01$) compared with non-pre-emptive SPK. Further, pre-emptive SPK conferred a significantly lower adjusted mortality risk [RR 0.50 ($p<0.001$)] [37].

Wiseman et al. reported an OPTN/UNOS analysis on type I diabetic recipients who received either a live donor kidney transplant ($n=1,381$) or an SPK ($n=5,441$). Overall, 2,027 patients were transplanted pre-emptively, including 1,529 SPK recipients. The remaining 4,795 patients were transplanted after initiation of chronic dialysis, including 3,912 SPK recipients (1,700 < 1 year of dialysis; 2,212 after 1–2 years of dialysis). Graft survival was improved in pre-emptive SPK (7-year unadjusted graft survival 77 %) as compared to either <1 year of dialysis SPK (70 %; $p=0.05$) or 1–2 years of dialysis SPK (73 %; $p<=0.02$). Patient survival was also improved in pre-emptive SPK (7-year unadjusted survival 89 %) as compared to either <1 year of dialysis SPK (84 %; $p=0.01$) or 1–2 years of dialysis SPK (84 %; $p<0.001$) [38].

31.4 Donor Selection

Since the results of SPK are strongly influenced by the quality of the donor, most transplant centres adopt a restrictive policy to accept pancreas grafts. However, if on one hand this policy is likely to improve the outcome of SPK in the individual patient, on the other, it widens the gap between the number of the patients on the waiting list and those who are actually transplanted. Expansion of criteria for donor acceptance should therefore be considered.

Most pancreas grafts are currently obtained from deceased, heart-beating, donors. The use of live donors has also been described [39], and donation after cardiac death is increasingly used especially in the USA [40] and in the UK [41].

The suitability of a pancreas donor is based on general criteria common to all organ procurements as well as on specific pancreas-related factors. Probably the single most relevant factor to determine pancreas suitability for transplantation is inspection by an

experienced pancreas transplant surgeon, despite being a subjective criterion that cannot be standardized. The prototype pancreas donor is a brain-dead donor, aged between 10 and 45 years, with a BMI $\leq$30 kg/m^2, who died for causes other than cerebrovascular [42, 43]. Additional factors that play a major role are duration of stay in the intensive care unit, use of high-dose vasopressors, history of cardiac arrest, and hypernatraemia. These parameters have also been used to construct risk scores for pancreas donation (i.e. the Pre-Procurement Pancreas Suitability Score [P-PASS] and the Pancreas Donor Risk Index [P-DRI]) [42, 44]. The predictive value of these scores, and hence their practical utility, remains to be determined.

Donor age is a very important variable. Very young donors are carefully considered because of the small size of the graft and the increased risk of thrombosis, because of the small size of the vessels. Most centres accept pancreas grafts from donors with a minimum weight of 30 kg. The use of donors older than 45 years, on the other hand, is known to increase the risk of technical graft failure [45].

Cause of death is another important factor. The "ideal" pancreas donor is a young trauma victim with no associated morbidity. Also young patients who died from intracranial bleeding, because of congenital cerebral aneurysm, are good pancreas donors. Death from ischemic stroke, instead, is associated with the presence of multiple comorbid factors, such as hypertension and atherosclerosis, that are known to negatively influence the result of SPK.

Hyperglycaemia, in the absence of history of diabetes, is often seen in brain-dead donors and, per se, does not contraindicate pancreas donation. Similarly, hyperamylasaemia does not necessarily correspond to pancreas damage in the absence of specific risk factors. Hyperamylasaemia is often caused by salivary gland trauma.

Vasopressors are commonly used in brain-dead donors to maintain satisfactory tissue perfusion. However, the use of powerful high-dose vasoconstrictor agents (e.g. epinephrine or norepinephrine) is considered a relative contraindication by many transplant surgeons. History of cardiac arrest, if short lived and successfully reversed, does not contraindicate pancreas donation.

Donor obesity is often considered a contraindication. In particular, grafts with fatty degeneration are considered more likely to develop posttransplant pancreatitis, thrombosis, and infection. Despite the lack of a clearly defined cutoff level, donor BMI above 30 kg/m^2 is usually considered a significant risk factor and donor BMI above 35 kg/m^2 an absolute contraindication.

Regarding organ allocation, AB0 group compatibility and negative crossmatch are usually required, while HLA matching is not critical for SPK transplants.

31.5 Surgical Techniques

31.5.1 Pancreas Procurement and Back-Table Preparation of the Graft

The University of Wisconsin solution, originally developed as a preservation solution for pancreas transplantation [46], remains the "gold standard" for preservation

of pancreas grafts. HTK [47] and Celsior [48] solutions, originally developed for cardioplegia, are also used for pancreas preservation. If cold ischaemia is maintained within 12 h, pancreas grafts are preserved equally well irrespective of the type of preservation solution.

Pancreas retrieval is usually performed in multiorgan donors. All suitable donors should be pancreas donors, irrespective of variations in hepatic vasculature. Exceptions to this rule can occur because of special needs of the liver recipient or organizational issues.

Techniques for pancreas procurement can be summarized into two main strategies: quick en bloc procurement after minimal normothermic dissection [49] and extensive warm dissection followed by individual graft retrieval [50]. The first technique is mandatory if the donor in unstable and is often preferred because of limited graft manipulation and lower risk of iatrogenic injury to both the pancreas and hepatic vasculature [49].

As previously mentioned, pancreas inspection and quality of visceral perfusion play a major role in determining pancreas suitability for transplantation. Grafts with fibrosis and/or calcification, intralobular fat, and severe oedema should be discarded.

With few exceptions, pancreas allografts are composed by the entire pancreas plus a duodenal segment. At the back table, the pancreas graft must be carefully prepared by cleaning excessive fat, preparing vascular pedicles, trimming duodenal segment, and removing the spleen.

Since the celiac trunk and the hepatic artery go with the liver, creation of a single anastomotic pedicle requires the use of a Y-bifurcated iliac graft, made of common, external, and internal donor iliac arteries. The peripheral branches of the Y-shaped graft are anastomosed end-to-end to the stumps of the superior mesenteric artery and the splenic artery. Despite the patency of one of these two large arteries that is usually sufficient to supply the entire pancreas graft and duodenal segment, variations in the origin of the dorsal pancreatic artery and intraparenchymal vasculature can produce segmental graft infarction after occlusion of one large arterial pedicle. To verify the presence of valid collateral circulation, a small amount of preservation solution can be injected in one of the two arteries. Brisk backflow from the other arterial pedicle, as well as outflow from the portal vein, indicates satisfactory collateral circulation. The absence of arterial backflow requires revascularization of the gastroduodenal artery [51].

The duodenal segment is trimmed at the appropriate length and closed by a stapler. Closures are reinforced and inverted. We prefer to place a Foley catheter in the duodenal segment to provide temporary drainage of pancreatic juice after reperfusion in order to avoid duodenal overdistension [49].

31.5.2 Graft Implantation

Most of the surgical challenges associated with pancreas transplantation revolve around the high risk of vascular thrombosis and the difficult management of exocrine secretions. Despite improved results, no surgical technique, and even no single

surgical step, has achieved universal acceptance [52]. The incision is usually a midline laparotomy, but the two grafts can also be transplanted through two separate iliac, hockey stick, incisions. The graft can be placed "head up" or "head down", in the pelvis, right flank region, or over the mesenteric root. Venous effluent can be achieved either in the portal or systemic circulation.

Typically, the pancreas is transplanted on the right side, because of the more convenient venous anatomy, and the kidney on the left iliac fossa. Ipsilateral SPK transplantation can also be accomplished, to spare one iliac axis or because of specific recipient needs. Exocrine secretions can be drained in the bladder or in the gut. Enteric drainage occurs in the small bowel either directly or through a Roux-en-Y loop. Newer techniques include direct anastomosis with recipient duodenum [53] or stomach [54]. Alleged advantages of these methods include direct access to donor duodenum for endoscopic biopsy, but concerns remain on safety, especially when recipient duodenum is involved, if allograft pancreatectomy becomes necessary.

Recently, we have described the technique for laparoscopic robot-assisted, pancreas transplantation including SPK transplantation [55, 56]. The advantages of a minimally invasive approach would seem obvious in the fragile diabetic recipient, but safety and efficacy of this newer technique need to be further assessed.

Kidney transplantation employs standard techniques, but if performed through a transperitoneal approach, the graft should be fixed in order to avoid twisting around the renal pedicle [57].

Cold ischaemia time exceeding 20 h has long been recognized a negative prognostic factor for the occurrence of surgical complications after pancreas transplantation. A growing burden of evidence shows that cold ischaemia time should actually be reduced to 12 h or less, especially when using less than ideal donors [43].

31.6 Postoperative Management and Outcome

31.6.1 Immunosuppression

Despite recent improvements, the results of pancreas transplantation continue to be challenged by high rejection rates [58]. Because of this concern, the use of T-cell depleting antibody induction is often employed.

Maintenance immunosuppression regimens are based on steroids, tacrolimus, and mycophenolate in more than 80 % of cases [59, 60]. The switching to cyclosporine and/or mammalian target of rapamycin is considered to reverse the side effects related to the standard regimen or under individual circumstances [61, 62].

31.6.2 Postoperative Care

After the transplant, recipients are monitored in the postanaesthesia care unit or intensive care unit. Ventilatory and haemodynamic assessment is paramount during recovery. A complete blood count, complete chemistry, coagulation profiles, chest

radiograph, and EKG are routinely obtained. Vital signs, oxygen saturation, and urine output are checked frequently. The first 24–48 h posttransplant is of overwhelming importance.

During this early period most of the efforts are focused to avoid vascular thrombosis. Although there is no agreed protocol for anticoagulant prophylaxis, most centres use early heparin infusion followed by oral antiplatelet agents. Antimicrobial, antifungal, and antiviral prophylaxis are also used routinely.

31.6.3 Major Posttransplant Complications

The propensity of the pancreas to vascular thrombosis, the need to manage exocrine secretions, and the high burden of medical comorbidities associated with diabetes and uraemia have all compounded the historical high rate of early complications after pancreas transplantation. Despite not all these complications are caused by a surgical error or misadventure, they are usually referred to as "surgical complications" because they often require surgical reintervention. Incidence has declined over time, but approximately 20 % of recipients still require at least one relaparotomy after pancreas transplantation [63]. Surgical complications remain the leading cause of early graft loss [64], now occurring in less than 5 % of pancreas transplants [63]. Graft survival, but not patient survival, is reduced by surgical complications [63].

The risk of major, potentially life-threatening, complications persists long term in fewer than 3 % of recipients in the form of pseudoaneurysm or arterioenteric fistula [65]. Chronic rejection may trigger these catastrophes [66, 67].

31.6.4 Follow-Up

Follow-up is key to the success of all solid organ transplants and in particular to SPK which couples the challenges of all other transplants (i.e. therapeutic noncompliance, infections, rejection, etc.) to the specific challenges posed by transplanting diabetic patients (i.e. presence of established secondary complications, risk of autoimmune reactivation, etc.). In a modern transplant centre, follow-up after SPK should be multidisciplinary.

In the early posttransplant period, follow-up focuses on prevention of vascular thrombosis, prevention and treatment of infections, achievement and maintenance of therapeutic drug levels, and monitoring for rejection. The lack of reliable markers for pancreas rejection remains a major issue. When pancreatic rejection is suspected, despite seemingly good renal function, pancreas biopsy is the only tool to achieve a reliable diagnosis.

In the long-term period, besides all needs associated with the follow-up of kidney transplant recipients, SPK recipients should be followed up regarding the evolution of secondary complications of diabetes. Death with functioning grafts remains a major issue in the long-term period. SPK recipients should therefore be strongly

encouraged to adopt a healthy lifestyle, in order to reduce their inherent high cardiovascular risk profile.

Recent evidence suggests also the need, besides standard immunologic follow-up, to closely monitor SPK with regard to de novo donor-specific anti-HLA antibodies [68].

Recurrence of autoimmunity is a further possibility that should be born in mind in this recipient population, as it could occur much more frequently than previously believed [31].

31.6.5 Outcome

Patient and graft survival rate for primary SPK transplant constantly improved over the last several years and now exceed 95 and 85 %, respectively [69]. The half-life of pancreas grafts now averages 16.7 years, achieving the longest duration found among extrarenal grafts [70] and nearly matching that of renal grafts from deceased donors [71].

Infection is the leading cause of death in the early posttransplant period, while cardiovascular events become prevalent long term. Other relevant causes of death are haemorrhage and malignancy [69].

Graft loss has a strong impact on the relative risk (RR) of recipient death. When the renal graft fails, the RR of recipient death increases almost 11-fold. When the pancreas fails, the RR of recipient death increases almost threefold. The RR of recipient death is also increased by patient age (≥45 years) and the need for pre-transplant dialysis or previous kidney transplant [69].

Vascular complications, intra-abdominal infections, and graft pancreatitis can cause pancreas loss, but the leading cause of pancreas failure remains rejection [72, 73]. Autoimmunity can also induce graft loss [74–77].

The diagnosis of pancreatic rejection can be proven only by core biopsy. A rise in serum creatinine can herald pancreatic rejection (the so-called sentinel kidney), but isolated pancreatic rejection has also been described [78]. An increase in serum amylase and lipase can be a further sign of pancreatic rejection, but it is not specific. Hyperglycaemia reflects islet destruction or severe isleitis and, as such, is a very late marker of rejection.

Antibody-mediated rejection (AMR) can also occur [79]. 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.

Recurrence of autoimmune disease can also occur despite immunosuppression [75, 80]. A possible interplay between AMR and autoimmune recurrence has also been described [80, 81]. Recurrence of autoimmunity occurs with isolated hyperglycaemia, without functional impairment of renal allograft or elevation of pancreatic enzymes. In these patients, islet cell autoantibodies against GAD, IA-2, and ZnT8 antigens have persisted, have increased, or have reappeared after pancreas transplantation [74, 75, 77]. These antibodies are accompanied by circulating

autoreactive CD4 or CD8 T cells. Biopsy shows insulitis and beta-cell loss without the features typically associated with allograft rejection. The rise of autoantibodies precedes hyperglycaemia by several years. Treatment options are nonspecific and include more sophisticated immunosuppressive therapies to target T cells, B cells, and autoantibodies. Plasmapheresis may also be used [74, 75].

31.6.6 Infections and Malignancies

Despite improved results, malignancies and bacterial, viral, and fungal infections remain a significant cause of mortality and morbidity [82].

The occurrence of viral infections may be facilitated to the fact that most diabetic patients have an impaired immune system and may not produce antibodies against cytomegalovirus and Epstein-Barr virus [83].

Posttransplant proliferative disorder (PTLD) is the most common malignancy after SPK, but the incidence of other cancers is also increased being three- to fourfold higher compared with matched and healthy population [84]. The cumulative incidence of PTLD from SRTR/Annual Data Report at 4 years is 0.9 % after SPK [58].

Polyomavirus (BK) can induce a severe nephropathy (BKVN) and is an important cause of renal graft loss following SPK. Routine screening for BK viraemia and an early treatment in case of positivity may protect from BKVN development. Recent data have shown that CNI and mycophenolate reduction and introduction of leflunomide may be important to block BK reactivation [85].

References

1. Diabetes Complications and Control Trial Research Group. The effect of intensive insulin treatment of diabetes on the development and progression of long-term complications of insulin dependent diabetes mellitus. N Engl J Med. 1993;329:977–86.
2. Kendall DM, Bergenstal RM. Limitations of nontransplant treatment options for Type 1 diabetes mellitus. In: Gruessner RWG, Sutherland DER, editors. Transplantation of the pancreas. New York: Springer; 2004. p. 29–38.
3. Allen KV, Walker JD. Microalbuminuria and mortality in long duration type 1 diabetes. Diabetes Care. 2003;26:2389–91.
4. Borch-Johnsen K, Kreiner S. Proteinuria: value as predictor of cardiovascular mortality in insulin dependent diabetes mellitus. Br Med J (Clin Res Ed). 1987;294:1651–4.
5. Warram JH, Laffel LMB, Ganda OP, Christlieb AR. Coronary artery disease is the major determinant of excess mortality in patients with insulin-dependent diabetes mellitus and persistent proteinuria. J Am Soc Nephrol. 1992;3:S104–10.
6. Borch-Johnsen K, Andersen PK, Deckert T. The effect of proteinuria on relative mortality in type I (insulin-dependent) diabetes. Diabetologia. 1985;28:590–6.
7. Wolfe RA, Ashby VB, Milford EL, Ojo AO, Ettenger RE, Agodoa LY, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. N Engl J Med. 1999;341:1725–30.
8. Kroslewski AS, Kosinski EJ, Warram JH, Leland OS, Busick EJ, Asmal AC, et al. Magnitude and determinants of coronary artery disease in juvenile-onset, insulin-dependent diabetes mellitus. Am J Cardiol. 1987;59:750–5.

9. Weinrauch LA, D'Elia JA, Healy RW, Gleason RE, Takacs FJ, Libertino JA, et al. Asymptomatic coronary artery disease: angiographically in diabetic patients before renal transplantation: relation of findings to postoperative survival. Ann Intern Med. 1978;88:346–8.
10. Braun WE, Phillips DF, Vidt DG, et al. Coronary artery disease in 100 diabetics with end-stage renal failure. Transplant Proc. 1984;16:603–7.
11. Grundy SM, Benjamin IJ, Burke GL, Chait A, Eckel RH, Howard BV, et al. Diabetes and cardiovascular disease: a statement of healthcare professionals from the American Heart Association. Circulation. 1999;100:1134–46.
12. Gruessner RW, Sutherland DE, Gruessner AC. Mortality assessment for pancreas transplants. Am J Transplant. 2004;4:2018–26.
13. Venstrom JM, McBride MA, Rother KI, Hirshberg B, Orchard TJ, Harlan DM. Survival after pancreas transplantation in patients with diabetes and preserved kidney function. JAMA. 2003;290:2817–23.
14. Tydén G, Tollemar J, Bolinder J. Combined pancreas and kidney transplantation improves survival in patients with end-stage diabetic nephropathy. Clin Transplant. 2000;14:505–8.
15. Becker BN, Brazy PC, Becker YT, Odorico JS, Pintar TJ, Collins BH, et al. Simultaneous pancreas-kidney transplantation reduces excess mortality in type I diabetic patients with end-stage renal disease. Kidney Int. 2000;57:2129–35.
16. Smets YF, Westendorp RG, van der Pjil JW, de Charro FT, Ringers J, de Fijter JW, et al. Effect of simultaneous pancreas- kidney transplantation on mortality of patients with type I diabetes mellitus and end-stage renal failure. Lancet. 1999;353:1915–9.
17. Ojo AO, Meier-Kriesche HU, Hanson JA, Leichtman A, Magee JC, Cibrik D, et al. The impact of simultaneous pancreas-kidney transplantation on long-term patient survival. Transplantation. 2001;71:82–90.
18. Navarro X, Kennedy WR, Aeppli D, Sutherland DE. Neuropathy and mortality in diabetes: influence of pancreas transplantation. Muscle Nerve. 1996;19:1009–16.
19. Shapiro R, Corry RJ, Thai N. Outcomes after pancreatic transplantation. In: Corry RJ, Shapiro R, editors. Pancreatic transplantation. New York: Informa Healthcare; 2007. p. 1–10.
20. Reddy KS, Stablein D, Taranto S, Stratta RJ, Johnston TD, Waid TH, et al. Long-term survival following simultaneous kidney pancreas transplantation versus kidney transplantation alone in patients with type 1 diabetes mellitus and renal failure. Am J Kidney Dis. 2003;41:464–70.
21. Robertson RP, Davis C, Larsen J, Stratta R, Sutherland DE, American Diabetes Association. Pancreas and islet transplantation in type 1 diabetes. Diabetes Care. 2006;29(4):935.
22. Kaufman DB, Sutherland DE. Simultaneous pancreas-kidney transplants are appropriate in insulin-treated candidates with uremia regardless of diabetes type. Clin J Am Soc Nephrol. 2011;6(5):957–9.
23. Boggi U, Rosati CM, Marchetti P. Follow-up of secondary diabetic complications after pancreas transplantation. Curr Opin Organ Transplant. 2013;18(1):102–10.
24. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2014;37 Suppl 1:S81–90.
25. www.idf.org
26. Kelly WD, Lillehei RC, Merkel FK, Idezuki Y, Goetz FC. Allotransplantation of the pancreas and duodenum along with the kidney in diabetic nephropathy. Surgery. 1967;61(6):827–37.
27. Gruessner RW, Gruessner AC. The current state of pancreas transplantation. Nat Rev Endocrinol. 2013;9(9):555–62.
28. Boggi U, Vistoli F, Amorese G, Giannarelli R, Coppelli A, Mariotti R, Rondinini L, Barsotti M, Signori S, De Lio N, Occhipinti M, Mangione E, Cantarovich D, Del Prato S, Mosca F, Marchetti P. Long-term (5 years) efficacy and safety of pancreas transplantation alone in type 1 diabetic patients. Transplantation. 2012;93(8):842–6.
29. Gruessner RW, Gruessner AC. Pancreas transplant alone: a procedure coming of age. Diabetes Care. 2013;36(8):2440–7.
30. Kim SJ, Smail N, Paraskevas S, Schiff J, Cantarovich M. Kidney function before pancreas transplant alone predicts subsequent risk of end-stage renal disease. Transplantation. 2014;97(6):675–80.

31. Boggi U, Vistoli F, Egidi FM, Marchetti P, De Lio N, Perrone V, Caniglia F, Signori S, Barsotti M, Bernini M, Occhipinti M, Focosi D, Amorese G. Transplantation of the pancreas. Curr Diab Rep. 2012;12(5):568–79.
32. White SA, Shaw JA, Sutherland DE. Pancreas transplantation. Lancet. 2009;373(9677): 1808–17.
33. Larsen JL. Pancreas transplantation: indications and consequences. Endocr Rev. 2004;25(6):919–46.
34. Orlando G, Stratta RJ, Light J. Pancreas transplantation for type 2 diabetes mellitus. Curr Opin Organ Transplant. 2011;16(1):110–5.
35. Grossi PA, Righi E, Gasperina DD, Donati D, Tozzi M, Mangini M, Astuti N, Cuffari S, Castelli P, Carcano G, Dionigi G, Boggi U, Costa AN, Dionigi R. Report of four simultaneous pancreas-kidney transplants in HIV-positive recipients with favorable outcomes. Am J Transplant. 2012;12(4):1039–45.
36. Israni AK, Feldman HI, Propert KJ, Leonard M, Mange KC. Impact of simultaneous kidney-pancreas transplant and timing of transplant on kidney allograft survival. Am J Transplant. 2005;5:374–82.
37. Becker BN, Rush SH, Dykstra DM, Becker YT, Port FK. Preemptive transplantation for patients with diabetes-related kidney disease. Arch Intern Med. 2006;166:44–8.
38. Wiseman AC, Huang E, Kamgar M, Bunnapradist S. The impact of pre-transplant dialysis on simultaneous pancreas-kidney versus living donor kidney transplant outcomes. Nephrol Dial Transplant. 2013;28:1047–58.
39. Boggi U, Amorese G, Marchetti P, Mosca F. Segmental live donor pancreas transplantation: review and critique of rationale, outcomes, and current recommendations. Clin Transplant. 2011;25:4–12.
40. Siskind E, Akerman M, Maloney C, Huntoon K, Alex A, Siskind T, Bhaskeran M, Ali N, Basu A, Molmenti E, Ortiz J. Pancreas transplantation from donors after cardiac death: an update of the UNOS database. Pancreas. 2014;43:544–7.
41. Johnson RJ, Bradbury LL, Martin K, Neuberger J, UK Transplant Registry. Organ donation and transplantation in the UK-the last decade: a report from the UK national transplant registry. Transplantation. 2014;97 Suppl 1:S1–27.
42. Finger EB, Radosevich DM, Dunn TB, Chinnakotla S, Sutherland DE, Matas AJ, Pruett TL, Kandaswamy R. A composite risk model for predicting technical failure in pancreas transplantation. Am J Transplant. 2013;13:1840–9.
43. Maglione M, Ploeg RJ, Friend PJ. Donor risk factors, retrieval technique, preservation and ischemia/reperfusion injury in pancreas transplantation. Curr Opin Organ Transplant. 2013;18:83–8.
44. Vinkers MT, Rahmel AO, Slot MC, Smits JM, Schareck WD. How to recognize a suitable pancreas donor: a Eurotransplant study of preprocurement factors. Transplant Proc. 2008;40:1275–8.
45. Gruessner AC, Barrou B, Jones J, Dunn DL, Moudry-Munns K, Najarian JS, Sutherland DE, Gruessner RW. Donor impact on outcome of bladder-drained pancreas transplants. Transplant Proc. 1993;25:3114–5.
46. Wahlberg JA, Love R, Landegaard L, Southard JH, Belzer FO. 72-hour preservation of the canine pancreas. Transplantation. 1987;43:5–8.
47. Fridell JA, Mangus RS, Powelson JA. Histidine-tryptophan-ketoglutarate for pancreas allograft preservation: the Indiana University experience. Am J Transplant. 2010;10:1284–9.
48. Boggi U, Vistoli F, Del Chiaro M, Signori S, Croce C, Pietrabissa A, Berchiolli R, Marchetti P, Del Prato S, Mosca F. Pancreas preservation with University of Wisconsin and Celsior solutions: a single-center, prospective, randomized pilot study. Transplantation. 2004;77: 1186–90.
49. Boggi U, Vistoli F, Del Chiaro M, Signori S, Pietrabissa A, Costa A, Bartolo TV, Catalano G, Marchetti P, Del Prato S, Rizzo G, Jovine E, Pinna AD, Filipponi F, Mosca F. A simplified technique for the en bloc procurement of abdominal organs that is suitable for pancreas and small-bowel transplantation. Surgery. 2004;135:629–41.

50. Wunderlich H, Brockmann JG, Voigt R, Rauchfuss F, Pascher A, Brose S, Binner C, Bittner H, Klar E, Commission of Organ Donation and Removal German Transplantation Society. DTG procurement guidelines in heart beating donors. Transpl Int. 2011;24:733–57.
51. Boggi U, Amorese G, Marchetti P. Surgical techniques of pancreas transplantation. In: Hakim NS, Stratta RJ, Gray D, Friend P, Colman A, editors. Pancreas, islet, and stem cell transplantation for diabetes. 2nd ed. Oxford: Oxford University Press; 2010. p. 111–35.
52. Demartines N, Schiesser M, Clavien PA. An evidence-based analysis of simultaneous pancreas-kidney and pancreas transplantation alone. Am J Transplant. 2005;5:2688–97.
53. De Roover A, Coimbra C, Detry O, Van Kemseke C, Squifflet JP, Honore P, Meurisse M. Pancreas graft drainage in recipient duodenum: preliminary experience. Transplantation. 2007;84:795–7.
54. Shokouh-Amiri H, Zakhary JM, Zibari GB. A novel technique of portal-endocrine and gastric-exocrine drainage in pancreatic transplantation. J Am Coll Surg. 2011;212:730–8.
55. Boggi U, Signori S, Vistoli F, D'Imporzano S, Amorese G, Consani G, et al. Laparoscopic robot-assisted pancreas transplantation: first world experience. Transplantation. 2012;93:201–6.
56. Boggi U, Signori S, Vistoli F, Amorese G, Consani G, De Lio N, et al. Current perspectives on laparoscopic robot-assisted pancreas and pancreas-kidney transplantation. Rev Diabet Stud. 2011;8:28–34.
57. West MS, Stevens RB, Metrakos P, Foshager MC, Jessurun J, Sutherland DE, Gruessner RW. Renal pedicle torsion after simultaneous kidney-pancreas transplantation. J Am Coll Surg. 1998;187:80–7.
58. OPTN/SRTR annual data report 2010/Pancreas. p. 34–52.
59. Heilman RL, Mazur MJ, Reddy KS. Immunosuppression in simultaneous pancreas-kidney transplantation: progress to date. Drugs. 2010;70:793–804.
60. Singh RP, Stratta RJ. Advances in immunosuppression for pancreas transplantation. Curr Opin Organ Transplant. 2008;13:79–84.
61. Matias P, Araujo MR, Romao JE, Abensur H, Noronha IL. Conversion to sirolimus in kidney-pancreas and pancreas transplantation. Transplant Proc. 2008;40:3601–5.
62. Egidi MF, Cowan PA, Naseer A, Gaber AO. Conversion to sirolimus in solid organ transplantation: a single-center experience. Transplant Proc. 2003;35:S131–7.
63. Banga N, Hadjianastassiou VG, Mamode N, Calder F, Olsburgh J, Drage M, et al. Outcome of surgical complications following simultaneous pancreas–kidney transplantation. Nephrol Dial Transplant. 2012;27:1658–63.
64. Fernandez-Cruz L, Ricart MJ, Astudillo E, Sabater L, Fondevila C, Prados M. Enteric drainage as primary procedure and after cystoenteric conversion in whole pancreaticoduodenal transplantation. Transplant Proc. 1997;29:643–4.
65. Fridell JA, Johnson MS, Goggins WC, Beduschi T, Mujtaba MA, Goble ML, et al. Vascular catastrophes following pancreas transplantation: an evolution in strategy at a single center. Clin Transplant. 2012;26:164–72.
66. Higgins PD, Umar RK, Parker RJ, DiMagno MJ. Massive lower gastrointestinal bleeding after rejection of pancreatic transplants. Nat Clin Pract Gastroenterol Hepatol. 2005;2:240–4.
67. Lopez NM, Jeon H, Ranjan D, Johnston TD. Atypical etiology of massive gastrointestinal bleeding: arterio-enteric fistula following enteric drained pancreas transplant. Am Surg. 2004;70:529–32.
68. Mittal S, Page SL, Friend PJ, Sharples EJ, Fuggle SV. De novo donor-specific HLA antibodies: biomarkers of pancreas transplant failure. Am J Transplant. 2014;14:1664–71.
69. Gruessner AC, Sutherland DER. In: Hakim NS, Stratta RJ, Gray D, Friend P, Colman A, editors. Pancreas-transplant outcomes for United States (US) cases as reported to the United Network for Organ Sharing (UNOS) and the International Pancreas Transplant Registry (IPTR). New York: Oxford University Press; 2010. p. 299–315.
70. Lodhi SA, Lamb KE, Meier-Kriesche HU. Solid organ allograft survival improvement in the United States: the long-term does not mirror the dramatic short-term success. Am J Transplant. 2011;11:1226–35.

71. Seron D, Moreso F, Arias M, Campistol JM, Curto J, Hernandez D, et al. Estimation of renal allograft half-life: fact or fiction? Nephrol Dial Transplant. 2011;26:3013–8.
72. Oberholzer J, Tzvetanov G, Benedetti E. Surgical complication of pancreas transplantation. In: Hakim NS, Stratta RJ, Gray D, Friend P, Colman A, editors. Pancreas, islet, and stem cell transplantation for diabetes. New York: Oxford University Press; 2010. p. 179–89.
73. Troxell ML, Koslin DB, Norman D, Rayill S, Mittalhenkle A. Pancreas allograft rejection: analysis of concurrent renal allograft biopsies and posttherapy follow-up biopsies. Transplantation. 2010;90:75–84.
74. Burke 3rd GW, Vendrame F, Pileggi A, Ciancio G, Reijonen H, Pugliese A. Recurrence of autoimmunity following pancreas transplantation. Curr Diabetes Rep. 2011;11:413–9.
75. Vendrame F, Pileggi A, Laughlin E, Allende G, Martin-Pagola A, Molano RD, et al. Recurrence of type 1 diabetes after simultaneous pancreas-kidney transplantation, despite immunosuppression, is associated with autoantibodies and pathogenic autoreactive CD4 T-cells. Diabetes. 2010;59:947–57.
76. Braghi S, Bonifacio E, Secchi A, Di Carlo V, Pozza G, Bosi E. Modulation of humoral islet autoimmunity by pancreas allotransplantation influences allograft outcome in patients with type 1 diabetes. Diabetes. 2000;49:218–24.
77. Occhipinti M, Lampasona V, Vistoli F, Bazzigaluppi E, Scavini M, Boggi U, et al. Zinc transporter 8 autoantibodies increase the predictive value of islet autoantibodies for function loss of technically successful solitary pancreas transplant. Transplantation. 2011;92:674–7.
78. Shapiro R, Jordan ML, Scantlebury VP, Vivas CA, Jain A, McCauley J, et al. Renal allograft rejection with normal renal function in simultaneous kidney/pancreas recipients: does dissynchronous rejection really exist? Transplantation. 2000;69:440–1.
79. Drachemberg CB, Torrealba JR, Nankivell BJ, Rangel EB, Bajema IM, Kim DU, et al. Guidelines for the diagnosis of antibody- mediated rejection in pancreas allografts-updated banff grading schema. Am J Transplant. 2011;11:1792–802.
80. Pugliese A, Reijonen HK, Nepom J, Burke 3rd GW. Recurrence of autoimmunity in pancreas transplant patients: research update. Diabetes Manag (Lond). 2011;1:229–38.
81. Porcheray F, DeVito J, Yeap BY, Xue L, Dargon I, Paine R, et al. Chronic humoral rejection of human kidney allografts associated with broad autoantibody response. Transplantation. 2010;89:1239–46.
82. Rostambeigi N, Kudva YC, John S, Mailankody S, Pedersen RA, Dean PG, et al. Epidemiology of infections requiring hospitalization during long-term follow-up of pancreas transplantation. Transplantation. 2010;89:1126–33.
83. Parsaik AK, Bhalla T, Dong M, Rostambeigi N, Dierkhising RA, Dean P, et al. Epidemiology of cytomegalovirus infection after pancreas transplantation. Transplantation. 2011;92:1044–50.
84. Girman P, Lipar K, Kocik M, Kriz J, Marada T, Saudek F. Neoplasm incidence in simultaneous pancreas and kidney transplantation: a single-center analysis. Transplant Proc. 2011;43:3288–91.
85. Mujtaba M, Fridell J, Sharfuddin A, Kandula P, Yaqub MS, Phillips CL, et al. BK virus nephropathy in simultaneous pancreas kidney transplant: a potentially preventable cause of kidney allograft loss. Clin Transplant. 2012;12:87–93.