Chapter 19
Kidney Transplantation and Kidney Pancreas Transplantation

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Introduction

Diabetes is a global health emergency, with 425 million people affected in 2017 and a projection for 629 million by 2045. Nearly half develop diabetic kidney disease, and its prevalence is rising progressively in parallel with the overall diabetes epidemic, primarily driven by type 2 diabetes [1]. In a recent report based on data from 142 countries, the global percentage of the prevalent end-stage renal disease (ESRD) patients with diabetes increased from 19.0% in 2000 to 29.7% in 2015 worldwide, while the percentage of incident ESRD patients due to diabetes increased from 22.1% to 31.3% [2]. Type 2 DM is now the leading cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD) worldwide [3] and accounts for nearly 95% of all cases of DKD [4]. According to the 2020 United States Renal Data System (USRDS), prevalent ESRD among all patients with a diagnosis of DM exceeded 300,000 in 2018 in the USA, representing ~38% of all patients on dialysis [5]. Similarly, data from the Organ Procurement and Transplantation Network/Scientific Registry of Transplant Recipients (OPTN/SRTR) show that nearly 40% of patients on transplant waiting list in the USA had DM in 2019 [6] (see Fig. 19.1).

Type 2 DM is a major risk factor for the development of cardiovascular (CV) and kidney disease and is responsible for a significant number of hospitalizations, morbidity, and mortality. Kidney transplant has emerged as the preferred mode of renal replacement for ESRD, including patients with diabetic kidney disease. Transplant

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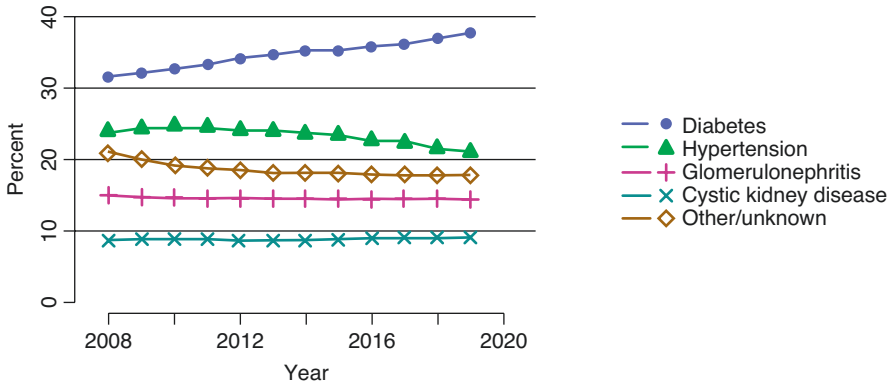

Fig. 19.1 Distribution of adults waiting for a kidney transplant by diagnosis. Candidates waiting for transplant at any time in the given year. Candidates listed at more than one center are counted once per listing. Active and inactive patients are included [6]

provides both better quality of life and survival advantage compared to dialysis [7, 8]. For example, receiving a deceased donor kidney increases a patient's chances of survival by twofold and a living-donor graft by fourfold compared to those who remain on the waiting list [9]. In an earlier analysis, transplant increased the projected life expectancy in kidney transplant recipients by 10 years compared with those who remained on dialysis [8].

Kidney and/or pancreatic transplantation has now proved to be the treatment of choice for those patients. Kidney and pancreas transplantation not only solves the problem of organ failure but also achieves insulin independence and reverses the metabolic complications of diabetes. Combined kidney and pancreas transplantation has the best long-term outcome in patients with advanced or end-stage kidney disease [7].

In the past, pancreatic transplant was not offered to type 2 DM patients. However, as later data showed that simultaneous pancreas-kidney (SPK) transplant has resulted in similar outcomes in both type 1 and type 2 DM patients, there is increasing acceptance of type 2 DKD patients for this modality. Still, pancreas transplant is rarely offered to type 2 DM patients; the rate of pancreas transplant in type 2 DM patients increased from 2% in 1995 to only 7% in 2010 [10]. There was some further modest increase after the 2014 revision in the pancreas allocation system (PAS) (see Fig. 19.2). According to the Organ Procurement and Transplantation Network and Scientific Registry of Transplant Recipients (OPTN/SRTR) 2019 annual report, the total number of pancreas transplants in 2019 was 1015, slightly lower than the previous year, but remained somewhat flat for the past 5 years [11]. Most of these involved simultaneous pancreas-kidney (SPK) transplants followed by pancreas-after-kidney (PAK) and pancreas transplant alone (PTA) [11].

Although the recently introduced agents, mainly the SGLT2 inhibitors, raise the expectations that they will further slow the progression of DKD to advanced stages, there will still be a need to implement renal replacement for many patients. The

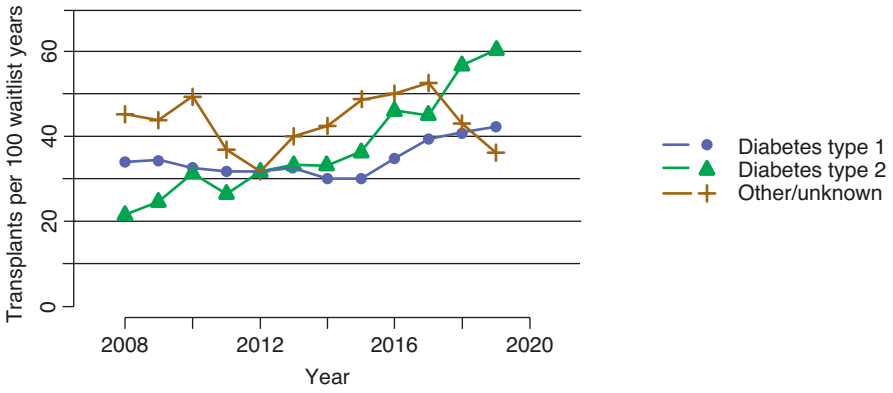

Fig. 19.2 Deceased donor pancreas transplant rates among adult wait-list candidates by diagnosis. Transplant rates are computed as the number of deceased donor transplants per 100 patient-years of wait time in a given year. Individual listings are counted separately [11]

purpose of this chapter is to briefly outline the transplant options for patients with advanced or end-stage diabetic kidney disease.

Transplant Options for Patients with Diabetic Kidney Disease

Diabetic kidney disease represents an increasing percentage of chronic kidney disease populations worldwide. The demand for renal replacement therapy is also on the rise as cases of diabetes have reached epidemic proportions [1, 2, 6]. Kidney transplantation has emerged as the clearly superior alternative for all ESRD of any etiology, especially for DKD, which carries a higher CVD risk and other comorbidities [1, 12–14]. Kidney transplantation is now an established modality and becoming increasingly available, with nearly 300,000 transplants performed since 1970 [9]. However, demand remains high such that barely a quarter of patients on the wait list receive a deceased donor kidney transplant within 5 years [6]. Although there is a recent trend toward a slightly increased availability of living-related donor kidneys, only a small fraction of patients benefit from this alternative [6].

Transplant options (Fig. 19.3) include kidney transplant alone, living or deceased donor (KT), simultaneous pancreas and kidney (SPK) transplant, and pancreas-after-kidney (PAK) transplant [7, 15, 16]. These treatment options generally offer markedly superior survival benefits for ESRD patients, including those with diabetic kidney disease. One-year KT survival in diabetic patients is now near 90% for deceased donors (DD) and 96% for living donors (LD) [7]. Pancreas transplantation has become increasingly successful in recent years due to advances in surgical outcomes and immunosuppression protocols [16–19]. One-year pancreas graft survival is now nearly 95% when performed as a simultaneous pancreas-kidney (SPK) transplant and 86% when performed as a pancreas after KT (PAK). In one single center,

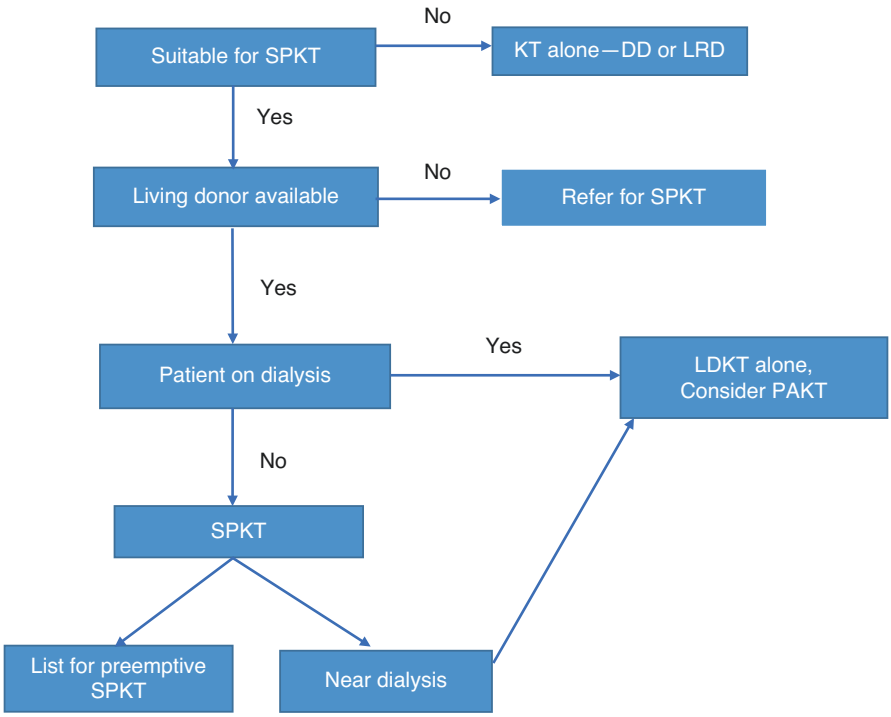

Fig. 19.3 Options for kidney transplant for patients with diabetic kidney disease. Adapted from A.C. Wiseman [16]. (*KT* kidney transplantation, *DD* deceased donor, *LRD* living-related donor, *SPKT* simultaneous pancreas-kidney transplantation, *LDKT* living-related kidney transplant, *PAKT* pancreas after kidney transplant)

mortality risk for diabetic patients was two- to threefold lower in those who received a pancreas transplant [6, 7, 20]. Other centers report similarly successful long-term outcomes [21, 22].

During the early years of transplantation, DKD was considered a relative contraindication for transplant because of the higher cardiovascular risk and obesity. This attitude has now reversed since Wolfe et al. demonstrated that renal transplantation provided a marked survival advantage for diabetic ESRD patients and reduced mortality by 73% compared with patients remaining on the wait list. The projected life expectancy was more pronounced for younger diabetics (presumed type 1 DM) with a gain of 17 years, and the gain was also significant even for patients older than 60 years (presumed type 2 DM) [8, 13]. Long-term follow-up analyses confirm superior outcomes and significant survival benefit for ESRD patients associated with type 1 DM [23].

The evidence supports that preemptive transplant is superior to dialysis or to transplant after initiation of dialysis and results in improved recipient survival [1, 3, 24]. Patients in the USA qualify for kidney transplant listing when their glomerular filtration rate (GFR) is <20 ml/min or when they have initiated maintenance

dialysis. Despite the distinct advantages of preemptive transplant, the rates remain disappointingly low in the USA [25]. Lack of clear guidelines on the timing of referral, pre-dialysis patient education, and socioeconomic factors are among the key barriers [25].

Transplant programs have considered obesity [body mass index (BMI) >30–35 kg/m2] as a relative contraindication for transplantation in diabetic patients because of inferior outcomes for both KT and SPK transplant, mainly due to surgical complications. Some centers view only morbid obesity (BMI >40 kg/m2) as an absolute contraindication. Recent advances in bariatric surgery can ameliorate this contraindication and make even obese type 2 DM patients eligible for transplantation [13].

Patient Selection and Kidney Transplant

For optimal outcomes, a careful pre-transplant evaluation and risk screening are essential. Each modality has its advantages and disadvantages depending on patient selection (Table 19.1). As the waiting list for kidney transplantation continues to grow, the need for selecting appropriate candidates for transplant becomes fundamental. To maximize the success rates of transplant, a careful review and evaluation of coexisting medical and psychosocial comorbidities should be performed to intervene, if possible, before the procedure [26].

It is important to evaluate patients carefully for contraindications including recent or active malignancy, active infection, advanced atherosclerotic cardiac and

Table 19.1 Comparison of transplant options for diabetic kidney disease

Modality	Pros	Cons
DDKT	Superior survival compared to dialysis options	Graft and patient survival not as good as other transplant options
LDKT	Better graft and patient survival; can be done before initiating dialysis or it reduces time on dialysis	Does not help with glycemic control
SPK	Achieves insulin independence; median pancreas graft survival of >10 years	More complex surgery with higher complication and mortality rates
PAK	Achieves insulin independence	Requires two separate surgeries, increased early post-op mortality after pancreas transplant
PTA	Achieves metabolic control, prevents microvascular complications including DKD	Suitable only for insulin-dependent diabetics without kidney disease
Islet cells	Prevents diabetic kidney disease, no surgery involved	Technique still not fully established engrafting is short-lived, requires repeat procedures

DDKT deceased donor kidney transplant, *LDKT* living donor kidney transplant, *SPK* simultaneous pancreas-kidney transplant, *PAK* pancreas after kidney transplant. Adapted from A. C. Wiseman [15]

vascular disease, alcohol-drug dependence, psychiatric disease, and morbid obesity [7, 13]. If significant coronary artery disease is present, transplantation can still proceed after appropriate therapy, which may include coronary artery revascularization. As noted above, severe obesity is no longer an absolute contraindication. Morbidly obese patients can become eligible for transplant after bariatric surgery [13].

The current guidelines suggest that transplant candidates should be evaluated carefully and in an unbiased multidisciplinary setting, involving physicians, surgeons, psychologists, social workers, financial counselors, and dietitians, and sometimes the patients. This process may take considerable resources and time depending on the extent of testing needed for each patient. At the end of the evaluation, patients should be discussed at a multidisciplinary Selection Committee for a consensus agreement on the final listing [27].

As the demand for kidney transplant is rising, there is a shortage of available kidneys [6]. Living donation accounts for one-third of kidney transplants performed in the USA, showing a remarkable increase in the annual number of living donors from 1988 to 2004, although there is a recent trend toward a decline [28–30]. Family members have usually been the main source of living donations, although unrelated donations from friends and coworkers have recently increased. Altruistic anonymous donations from strangers are also increasing. Potential living donors need a comprehensive and cautious evaluation to minimize the risks in a healthy altruistic donor who is willing to undertake a major surgical procedure to help another [31]. Kidney paired donation, a national United Network for Organ Sharing (UNOS)-sponsored swapping of incompatible donors, has facilitated multiple living donor transplants, but the impact on the number of transplants has been modest [6, 28, 29].

Pancreas Transplantation

The first human pancreas transplant was performed in 1966 by Dr. Lillehei at the University of Minnesota [32]. The procedure was performed simultaneously with a kidney transplant in a young female with diabetic kidney disease. Unfortunately, the patient could remain insulin-free for only a few weeks. Although other pancreas transplants were performed over the next few years, the success rates were initially low. But later improvements in surgical techniques, immunosuppressive medications, and organ donor management have allowed pancreatic transplantation to become a well-accepted and commonly performed procedure [21].

Pancreas transplantation in conjunction with kidney transplantation, either simultaneously or after kidney transplantation, has proved valuable especially for DKD patients with type 1 DM and for some type 2 patients as well [7, 17, 33]. Pancreas transplant alone in type 1 DM patients before the onset of kidney disease may be particularly helpful in preventing kidney disease and other microvascular complications of diabetes and avoid the need for renal replacement [34, 35]. Based on 2004 to 2015 data, patient survival rates for SPK, PAK, or PTA ranged from 96

to 99% at 1 year, 89 to 91% at 5 years, and 70 to 80% at 10 years postoperatively [20].

Pancreatic transplantation can achieve improvements in metabolic disorders, including glucose and glucagon metabolism. Secondary complications of diabetes also show improvement, including improvement of left ventricular function and reversal of diastolic dysfunction [36]. Improvements in DKD [37], peripheral and autonomic diabetic neuropathy, possible diabetic retinopathy [37, 38], and serum triglyceride and low-density lipoproteins are also among the expected benefits [39].

Simultaneous pancreas-kidney (SPK) transplant initially carries a high mortality risk relative to living donor kidney recipients through 18 months posttransplantation, likely related to the surgical procedure complications. But the risk improved after the early postoperative period with better long-term outcomes [40]. A UNOS database review of all adult pancreas and kidney-pancreas transplants between 1996 and 2012 showed that graft survival was the best in adults 40–49 years of age [40].

Indications for Pancreas Transplants

The most common indication for a pancreatic transplant is insulin-dependent diabetes mellitus (IDDM). In most cases, patients have classic type 1 diabetes mellitus, an autoimmune disease with the presence of anti-insulin or anti-islet cell antibodies. Patients who develop IDDM from previous pancreatic resections or chronic pancreatitis have also received pancreas or islet cell transplants [41–43]. Many of these patients will have complications of IDDM, including hypoglycemic unawareness, diabetic ketoacidosis, as well as other organ sequelae such as kidney disease, retinopathy, and neuropathy [38, 39].

In the past, type 2 diabetes mellitus was considered a contraindication for pancreatic transplant, despite its proven success in type 1 diabetics. The presence of considerable overlap of clinical presentation of both types especially in the setting of renal failure, over-reliance on the presence of detectable C peptide, which is no longer considered reliable in determining DM type, and incomplete understanding of the pathogenesis were probably the main barriers [44]. Recently, there has been recognition of adult-onset diabetes that is insulin responsive [45–47]. Although these patients may previously have been characterized as type 2 diabetics, they show features of type 1 patients. They often are not obese, and they develop ketoacidosis and retinopathy. Some have even demonstrated late onset of insulin antibody development. Syndromes such as latent autoimmune diabetes in adults (LADA) or maturity-onset diabetes of the young (MODY) fall in this category [1, 45–48]. Such patients were previously classified as type 1½ diabetics, but recognition of these syndromes would allow these patients to benefit from a pancreas transplant as well. These diabetes variants clinically behave similarly to type 1 diabetes and benefit from pancreas or islet cell transplantation. There is growing evidence that these specific categories of type 2 diabetes patients with overlapping features of type 1

diabetes may benefit from a pancreas and kidney transplant. Increasing numbers of transplants are now offered to such patients [13, 41, 49, 50].

In most instances, pancreas transplants are performed in conjunction with a kidney transplant, either simultaneous (SPK) or pancreas after kidney (PAK), with good success rates [13, 33, 51]. The presence of diabetic renal disease with a GFR of less than 20 mL/min/1.73 m^2 or with the need to initiate dialysis is an indication for a kidney transplant as well.

The workup for a transplant candidate is exhaustive and like that of the kidney transplant recipient (see above) may consume considerable time and effort. Identification and management of the various sequelae of diabetes before the planned surgery are essential to minimize the risk of perioperative complications, including graft failure, infection, and death. In most centers, candidates are usually younger (<50 years of age) and non-obese (BMI <30). Results of pancreas transplants have not been as good in older or obese patients [52, 53].

Pancreatic Islet Cell Transplantation

Pancreas alone or islet cell transplant has emerged as another option for type 1 diabetics or MODY or LADA cases without renal disease. Successful pancreas transplant or beta islet cell replacement achieves excellent glycemic control and prevents the microvascular complications of diabetes including retinopathy, neuropathy, and kidney disease [34, 35, 54, 55]. There has been a long-standing interest in islet cell replacement since the turn of the nineteenth century, but the modality has not been clinically feasible until the development of the Edmonton Protocol in 2000 [56]. The harvested cells are transplanted via the portal vein and engraft in the liver and can achieve insulin independency. However, many challenges remain. Often, repeat islet cell infusions are necessary. Harvesting adequate numbers of cells is inefficient and often requires multiple donors. In the case of non-autologous transplants, immune reactivity and the need for anti-rejection treatment may be a problem [11, 56, 57]. There is ongoing active research in multiple fronts, including genetically modified islet cells, encapsulating islet cells in protected lattices, xenotransplants using genetically modified porcine cells, or using pluripotent stem cells [56, 58, 59]. With continued progress in this non-surgical technique, we can imagine a breakthrough in the treatment of diabetes and preventing its devastating complications including kidney disease.

Posttransplant Diabetes Mellitus (PTDM)

A major complication of kidney transplantation is the development of posttransplant posttransplant diabetes mellitus, which poses an important risk factor for cardiovascular disease and other diabetic complications, including kidney disease after transplantation [60, 61]. New onset diabetes mellitus in the posttransplantation setting (PTDM), regardless of the timing of detection or whether it was present undetected prior to transplantation or not, develops in 10–40% of patients [62–64] (see Fig. 19.4).

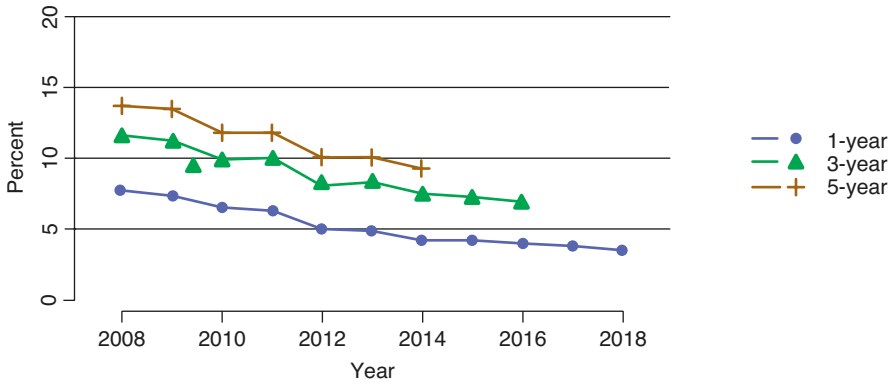

Fig. 19.4 Posttransplant diabetes among adult kidney transplant recipients. Percentage of adult deceased donor kidney recipients who were nondiabetic at transplant and developed diabetes post-transplant. Posttransplant diabetes is reported on the Transplant Recipient Follow-up form. Death and graft failure are treated as competing events [6]

Multiple factors contribute to the increased risk of PTDM. Immunosuppressive medications including steroids, calcineurin inhibitors, and mammalian target of rapamycin inhibitors are the main offenders. Higher doses of steroids have been associated with increased risk of PTDM. Both tacrolimus and cyclosporine also can increase the risk of PTDM, with a higher risk associated with tacrolimus than cyclosporine [64]. Other factors predisposing to PTDM include pre-transplant impaired glucose tolerance [65], obesity [66], hypomagnesemia [67], increased age (≥40 to 45 years), African American race, and deceased donor kidney transplantation [63, 65, 66, 68].

Posttransplantation diabetes mellitus (PTDM) leads to increased rates of cardiovascular disease mortality [68, 69], graft rejection, and decreased survival. Diabetic complications, such as ketoacidosis, hyperosmolar hyperglycemic state, neuropathy, diabetic kidney disease, and infection, can also occur [68, 70]. Often glycemic control can be achieved successfully using oral agents, especially dipeptidyl peptidase-4 (DPP-4) [71, 72]. Similarly, a recent meta-analysis showed that SGLT2 inhibitors effectively lowered HbA1c, reduced body weight, and helped preserve kidney function in transplant patients with PTDM and good kidney function without adverse events [73]. Optimal glycemic control and cardiovascular risk management improved outcomes markedly since 1996 [70, 74].

Summary and Conclusions

When measures to forestall kidney disease fail and patients reach advanced stages requiring renal replacement therapy, transplantation is distinctly superior to either peritoneal or hemodialysis. Transplant options include deceased donor or living donor kidney or combined pancreas and kidney transplant (simultaneous or

pancreas after kidney transplantation). Simultaneous pancreas-kidney transplant replaces kidney function and corrects the underlying metabolic disorder and affords the best survival advantage in the long run despite an initial increase in postsurgical mortality. Pancreas transplant alone is an option for type 1 and other forms of insulin-dependent diabetes patients and can prevent serious microvascular complications of diabetes, including kidney disease. Pancreatic islet cell transplantation is a nonsurgical technique with various configurations in experimental stages that promise optimal insulin independence but is not yet widely available clinically.

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