

Transplantation in Diabetic Kidney Failure Patients: Modalities, Outcomes, and Clinical Management

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ABSTRACT

Diabetes mellitus (DM) is a common and devastating disease, affecting up to 19.3 million Americans. It is the leading cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD) in the United States. Diabetic patients with ESRD have a high incidence of cardiovascular disease and death. For those kidney transplant patients with no history of DM prior to transplantation, the development of new onset diabetes after transplantation (NODAT) also poses a serious threat to both graft and patient survival. Kidney transplantation is the best renal replacement option for diabetic ESRD and has the potential to halt the progression of cardiovascular diseases. Early referral for transplant evaluation is essential for pre-emptive or early kidney transplantation in this cohort of patients. In type 1 DM patients with ESRD, simultaneous pancreas and kidney transplantation (SPK) should be encouraged; and in patients

facing prolonged waiting time for SPK transplantation but with an available living donor, living donor kidney transplantation followed by pancreas after kidney transplantation (PAK) is a suitable alternative. Islet transplantation in type 1 diabetics is deemed experimental by Medicare, and easy access to this modality remains restricted to qualified patients enrolled in clinical trials or with private insurance. The optimal management of kidney transplant patients with pre-existent DM or NODAT involves a multi-pronged approach consisting of pharmacological and nonpharmacological intervention to address all potential cardiovascular risk factors such as glycemic and lipid control, blood pressure control, weight loss, and smoking cessation. Finally, re-transplantation should be recommended in suitable kidney transplant patients when the kidney allograft demonstrates continuous and progressive decline in function.

Diabetes mellitus (DM) affects an estimated 19.3 million American adults with a prevalence of 9.3% (1). Its incidence continues to increase, particularly in the developing countries, and it is estimated that by 2025, 300 million people worldwide will be affected by this condition (2). DM is a strong risk factor for cardiovascular disease, chronic kidney disease (CKD), and premature death in the adult population (3–5). In fact, diabetic kidney disease occurs in 20–40% of patients with DM and is the leading cause of CKD and end-stage renal disease (ESRD) in the United States, accounting for nearly 45% of the dialysis patient population (6–8). In patients with both DM and CKD, the incidence of various cardiovascular complications and death is much higher than either condition alone (5,8).

Most diabetic patients will die of cardiovascular events prior to developing CKD or progressing to ESRD. For those who develop diabetic nephropathy, as evidenced by the appearance of microalbuminuria and decline in glomerular filtration rate (GFR), with eventual progression to ESRD, kidney transplantation

is the renal replacement therapy of choice. In type 1 diabetics with ESRD, simultaneous pancreas and kidney (SPK), or pancreas after kidney (PAK) transplantation are feasible options for qualified individuals whereas islet transplantation remains experimental at this time (9,10).

In patients without previous history of DM, any form of solid organ transplantation constitutes a risk factor for the development of new onset diabetes after transplantation (NODAT) (11). The development of NODAT portends an additional cardiovascular risk to transplant patients in general and to kidney transplant patients in particular (12,13).

Diabetes mellitus, present prior to or developing after kidney transplantation, represents a unique challenge to kidney transplant patients. In this review, we will focus our discussion on kidney transplantation as the treatment for diabetic ESRD patients, the effects of new onset diabetes after kidney transplantation, and on pancreas transplantation in type 1 DM patients.

Progression of Diabetic Chronic Kidney Disease and the Timing of Kidney Transplantation

Historically, 20–40% of diabetic patients develop diabetic nephropathy over a period of 25 years from the onset of disease, and 5–15% progress to ESRD (14–16).

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Besides genetic risk factors, hypertension, and hyperglycemia are the two most important risk factors for the development and subsequent progression of diabetic CKD (17–22). Aggressive lowering of blood pressure to 130/80 mmHg or less with the use of an angiotensin-converting enzyme inhibitor (ACEI) and/or angiotensin II receptor blocker (ARB) and strict glucose control, targeting HbA_{1c} to near normal (< 7%), appear to slow the progression of diabetic CKD (20,21,23,24). Nevertheless, a portion of patients will experience progressive decline in renal function and subsequent ESRD (22). Ultimately, these patients will require life-sustaining, long-term renal replacement therapy, either in the form of dialysis or kidney transplantation.

As in any other patient with CKD, the preparation for renal replacement therapy of diabetic patients requires focused patient education and timely referral to the nephrologist, vascular surgeon, and transplant specialist. Delayed referral for specialized care is common and results in poor pre-ESRD care, whereas timely referral improves the likelihood of pre-emptive or early (i.e., within the first 2 years of dialysis therapy) kidney transplantation (25–27). The choice of dialysis or kidney transplantation depends on many factors, including timely recognition of continued decline in renal function, resource availability, and patient co-morbidity. In the United States, the overwhelming majority of incident diabetic patients with ESRD will be initiated on renal replacement therapy in the form of hemodialysis, a phenomenon that is not exclusive to diabetic patients (8).

Diabetic CKD patients experience a high incidence of cardiovascular events and death that is further increased after they begin dialysis therapy (5,8,28). Kidney transplantation provides a better alternative when compared with dialysis as far as overall and cardiovascular mortality is concerned, a benefit that is particularly enjoyed by both type 1 and 2 diabetics. In a landmark study, Wolfe et al., examined at a national level the mortality among ESRD patients wait-listed for a kidney transplant when compared with that of ESRD patients who received a deceased donor kidney transplant (29). Kidney transplantation was associated with a significantly lower risk of death 18 months after transplantation (relative risk, 0.32, 95% CI 0.30, 0.35) with survival benefit clearly demonstrable 244 days after transplantation. The projected increase in life expectancy by transplantation was 10 years on average across all kidney transplant patients; of note, this survival advantage was particularly strong in diabetic ESRD patients, mainly because of their poorer survival on dialysis. Other investigators from different parts of the world have shown similar findings supporting the reproducibility of Wolfe's findings (30,31). A reduction in cardiovascular risk is the main reason for the survival advantage conferred by kidney transplantation (28,32).

The optimal timing for kidney transplantation in a diabetic patient with advanced CKD and/or ESRD is largely a matter of availability of a donor kidney. Avoiding dialysis or at least limiting its duration to no more than 180 days is associated with better post-transplant outcome and should be strongly recommended (33–35). Mange et al. showed that living donor kidney transplant

recipients without previous history of dialysis treatment had a 52% reduction in risk of graft failure within the first year after transplantation, when compared with those who were on dialysis at the time of transplantation ($p = 0.002$), with further reduction of risk during subsequent years following transplantation (82% in second year and 86% thereafter, respectively, $p = 0.001$) (33). Mange further observed that longer duration of dialysis treatment prior to transplantation was associated with increased risk for acute rejection within the first 6 months of transplantation.

In a subsequent study, Kasiske et al. demonstrated similar findings in patients receiving a deceased donor kidney transplant (25% risk reduction in graft failure for pre-emptive kidney transplant recipients when compared with those patients who had initiated dialysis prior to kidney transplantation) (36). More importantly, according to those investigators, the pre-emptive kidney transplantation resulted in improvement of patient survival (26% and 31% risk reduction in patient death for deceased and living donor kidney transplant recipients, respectively). More recently, Becker et al. investigated the benefit of pre-emptive kidney transplantation in type 1 and 2 diabetic ESRD population (37). The benefit of pre-emptive transplantation in this patient population regarding patient and graft survival was only observed after living donor kidney or SPK transplantation.

Thus, it is important to emphasize the advantage of pre-emptive living donor kidney transplantation in diabetic ESRD patients. Since diabetic patients come to receive medical attention much earlier than patients with nondiabetic CKD, early screening for kidney disease should be part of routine care for diabetic patients which consists of measurement of both microalbuminuria and serum creatinine (38). Once kidney disease is detected, periodic and ongoing monitoring of GFR becomes one of the most important aspects of patient care with regard to slowing the progression to ESRD and preparing for pre-emptive living donor kidney transplantation (27,39).

As more than 86,000 patients with ESRD are currently waiting for a kidney transplant and a little more than 13,000 kidney transplants are performed annually in the United States, the waiting time for a deceased donor kidney transplant has remained stagnant across the nation with a median time of three or more years (40). The avoidance of dialysis or shortening the length of dialysis is only possible if patients with CKD are referred to nephrologists and/or transplant centers when estimated GFR (eGFR) is around 30 ml/min, with the goal of listing the patient as soon as the eGFR declines to an average value of 20 ml/min or less, the UNOS requirement for placement in the renal transplant waiting list in the United States.

Under most circumstances, however, pre-emptive kidney transplantation is more likely to occur with a living donor as there is no waiting time involved. Discussion of the benefits of pre-emptive living donor kidney transplantation, and encouraging appropriate recipient candidates to search for potential living donors should be considered as part of a transplant evaluation process.

Management of Diabetic ESRD Patients after Kidney Transplantation

Although kidney transplantation is the superior treatment modality for patients with ESRD, the survival of kidney transplant patients remains inferior to that of the general population in part because of the accumulated cardiovascular burden and CKD vintage (41,42). The same cardiovascular risk factors that are relevant in the general population remain relevant in kidney transplant patients (43,44). In particular, the presence of DM and cardiovascular disease prior to kidney transplantation represents the most important predictors for cardiovascular events and all-cause mortality after kidney transplantation (45–47). In a cohort of 933 first-time kidney transplant patients, Cosio et al., showed that when compared with nondiabetic kidney transplant patients, kidney transplant patients with history of DM had a significantly higher incidence of post-transplant cardiovascular events (25% vs. 7.4%, $p < 0.0001$), cardiovascular mortality (12% vs. 1.1%, $p < 0.0001$) and all-cause mortality (19.3% vs. 6.1%, $p < 0.0001$) (45). Aalten et al. from the Netherlands showed similar findings in that pretransplant diabetic nephropathy was associated with a more than three times higher risk of having post-transplant cardiovascular events (46). It appeared that the high cardiovascular burden in DM patients before kidney transplantation was the driving force for persistence of elevated cardiovascular events observed after kidney transplantation.

It is important to point out that the incidence of cardiovascular events and death is highest in the first 3 months after kidney transplantation (29,44–46,48). This has been attributed to the fact that prolonged CKD and ESRD markedly increase cardiovascular risk, and multiple other comorbid conditions (43,49). Furthermore, despite the improvement in cardiovascular risks observed in patients following kidney transplantation, newer transplant-related risk factors such as immunosuppressive drugs, and inflammation due to opportunistic infection, particularly cytomegalovirus infection, perpetuate the high cardiovascular risk status of the kidney transplant patient population (48,50). The fact that the majority of kidney transplant patients will have a mild to moderate degree of CKD makes matters worse (51,52).

The role of immunosuppressive drugs on promoting cardiovascular risks has been well-documented (53). For example, the use of steroids, calcineurin inhibitors (CNIs) such as cyclosporine and tacrolimus, and more recently sirolimus can all contribute to and exacerbate hypercholesterolemia and hypertriglyceridemia that are already highly prevalent in kidney transplant patients (54–56). Hypertension, another conventional cardiovascular risk factor, is present in over 75% of kidney transplant patients, and its control is influenced negatively by steroids and CNIs (50,57). Both hyperlipidemia and hypertension are associated with reduced renal allograft survival in addition to increased risk for cardiovascular disease (58,59). For each 10 mmHg incremental rise in SBP, the risk for death and graft failure increases by 18% and 17%, respectively (59). In diabetic ESRD

patients, glycemic control tends to get worse and difficult to manage shortly after kidney transplantation. Insulin requirement may increase and oral hypoglycemic agents may fail, mostly because of increased insulin resistance and impaired insulin secretion associated with the use of steroids and CNIs (60–62).

At the present time, any improvement in cardiovascular disease risk in diabetic kidney transplant patients hinges on the appropriated management of conventional cardiovascular risk factors. The use of statins, possibly early after kidney transplantation, to lower LDL cholesterol has been shown to reduce cardiac death, nonfatal myocardial infarction, proteinuria, and interstitial fibrosis in the kidney allograft recipient (63–67). As most statins and CNIs are metabolized through the same cytochrome P450 system (CP3A4), attention should be paid to an increased frequency of rhabdomyolysis because of accumulation of statins in plasma with the use of CNIs (68). The reduction of LDL cholesterol to less than 100 mg/dl is generally recommended, but for diabetic kidney transplant recipients with history of pre-existent cardiovascular disease, a goal of LDL cholesterol of less than 70 mg/dl may be optimal (56,69).

Blood pressure control had to target a goal of $\leq 130/80$ mmHg or $\leq 125/70$ mmHg in the setting of established proteinuria (70). The choice of various anti-hypertensive agents often depends on the type of patients and the timing following kidney transplantation (71). Calcium channel blockers (CCB) are widely used as first-line therapy, particularly early post-transplantation, to counteract the vasoconstrictive effects of CNIs (57). While the use of ACEI and ARB is becoming more widespread their renal protective role, beyond decreasing proteinuria, has not been universally documented in kidney transplant patients (72–74). Glycemic control should target HbA_{1c} of less than 7% and fasting plasma glucose of 90–130 mg/dl (7,75). The use of various oral hypoglycemic agents and/or insulin depends on pre-transplant DM history. Referral to an endocrinologist is highly recommended.

It is important to emphasize that, in addition to the aforementioned pharmacological interventions to improve cardiovascular risk factors, lifestyle modification including dietary precautions, increasing physical exercise, weight loss, and smoking cessation should be strongly recommended, although the adherence to lifestyle modification is notoriously poor (76–81).

New Onset Diabetes after Kidney Transplantation

Patients with no history of DM prior to the transplantation are at risk of developing NODAT. Kasiske et al. studied 11,659 Medicare beneficiaries of first kidney transplant recipients and found a cumulative incidence of NODAT of 9.1%, 16%, and 24% at 3, 12, and 24 months after transplantation, respectively (11). Woodard et al. compared the incidence of NODAT between transplanted kidney patients and wait-listed nondiabetic ESRD kidney transplant candidates. They found that the cumulative incidence of NODAT more

than doubled when compared with pretransplantation level (82). In both studies, the risk of NODAT was highest in the first year after transplantation, although the risk remains elevated through the late post-transplant period (83). The development of NODAT increases the risk for cardiovascular events and the mortality following kidney transplantation (Fig. 1A,B) (12,13).

In addition to overt NODAT, kidney transplant recipients are at a greater risk for insulin resistance with a significantly high proportion of them having impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG), compared to the general population (84–86). IFG, a potential precursor of overt DM, occurs in about 26% of the US adult population and is associated with other cardiovascular risk factors (1,87,88). It has been suggested that IFG is a surrogate marker of insulin resistance that is ultimately responsible for the adverse cardiovascular outcome (89).

Besides traditional risk factors involved in pretransplant diabetes mellitus, the use of immunosuppressive drugs plays a major role in the genesis of NODAT and IGT (11,90). Steroids cause insulin resistance, CNIs impair secretion of insulin, and sirolimus decreases

insulin sensitivity (60–62,91). More recently, the use of steroid-free immunosuppression appears to have decreased the risk of NODAT (Fig. 2) (92–95). Nevertheless, modification of immunosuppression purely for the purpose of decreasing the risk of NODAT has to be balanced with the need of preventing graft rejection, as acute rejection may increase in steroid-free immunosuppression and has a stronger deleterious effect on graft survival (93,96).

The early detection of impaired glucose metabolism and NODAT in kidney transplant patients has been advocated by many investigators (86,97). Whether early detection leads to long-term graft and patient survival remains to be determined. Therapeutic intervention for patients who developed NODAT should include lifestyle modification, the use of oral hypoglycemic agents and/or insulin (75).

Pancreas Transplantation in Diabetic ESRD Patients

For type 1 and, rarely, type 2 diabetic patients, pancreas transplantation is also an option (98). Pancreas transplantation can be performed either at the same time of kidney transplantation (SPK transplantation) or after kidney transplantation (PAK transplantation). Pancreas transplantation can also be performed in type 1 DM patients without evidence of nephropathy (pancreas transplantation alone), and islet transplantation can be carried out before or after kidney transplantation. These last two subjects are beyond the scope of this review and will not be discussed further.

In a registry data analysis, Ojo et al. compared patient survival between comparable type 1 diabetic ESRD patients who received SPK, and living or deceased donor kidney transplant alone. Patients with SPK had better survival when compared with deceased but not to living donor kidney transplant alone recipients (99). When those patients who received SPK or kidney alone using contralateral kidneys from the same deceased donor were compared, the survival advantage of SPK was no longer observed (100).

In studies where SPK transplantation has resulted in long-term improvement of patient survival, pancreas

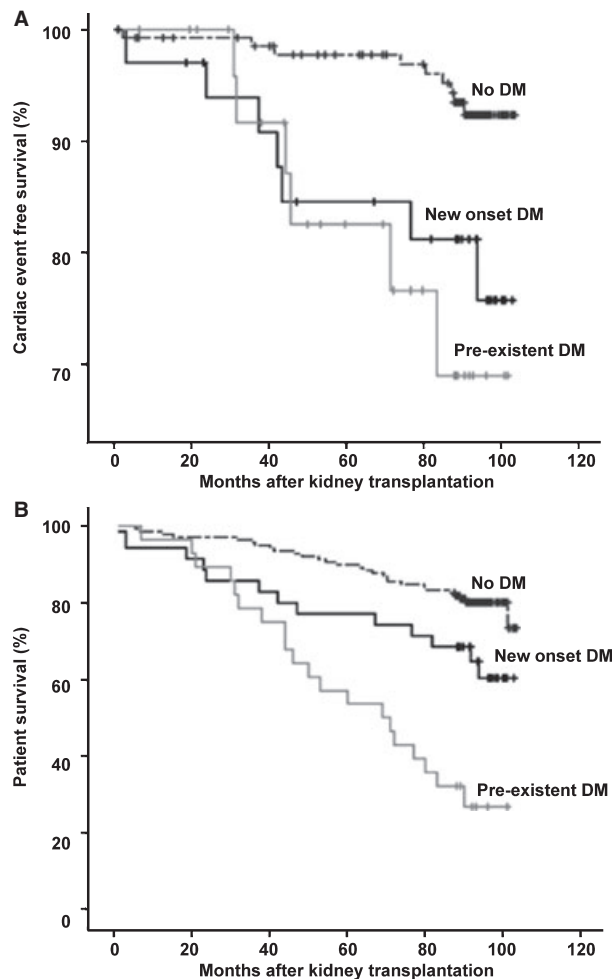


Fig. 1. Kaplan–Meier estimates of cardiac event-free survival (A) and patient survival (B) in renal transplant recipients according to the presence or absence of pre-existent diabetes, new onset diabetes. Adapted from Hjelmseth et al. with permission (13).

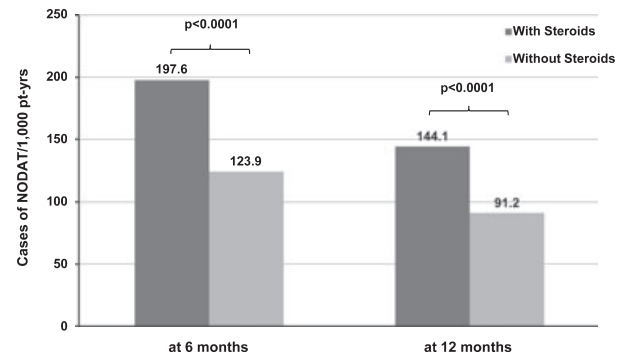


Fig. 2. Cumulative incidence of new onset diabetes in a national cohort of kidney transplant recipients discharged on steroid-free immunosuppressive regimens (96).

allograft survival played an important role (101,102). In a recent study of more than 3000 SPK patients followed for a maximum of 18 years, Morath et al., showed superior patient survival for SPK patients when compared with living donor kidney transplant alone patients beyond the 10th year after transplantation (hazard ratio 0.55, $p = 0.005$) (103). For patients who undergo PAK transplantation, the patient survival may be worse than those patients treated with conventional therapy, although one recent study showed otherwise (104,105).

On the contrary, successful pancreas transplantation does improve metabolic control and the cardiovascular risk profile, and can potentially reverse diabetic end organ damage as demonstrated by many investigators (106–110). In addition, the improvement in quality of life (QOL) will play an important role in determining the utility of pancreas transplantation. Several QOL studies have shown that when pancreas transplantation was successful, patients reported improvement in QOL when compared with type 1 diabetics who received a kidney transplant alone (111,112).

It is therefore safe to say that pancreas transplantation is a suitable option for type 1 diabetic ESRD patients. SPK transplantation should be discussed as one of the treatment options for type 1 diabetic ESRD patients, and equally encouraged as living donor kidney transplantation to qualified candidates.

Management of Failing Graft and Retransplantation in Diabetic Patients

Kidney graft failure represents a serious challenge to the transplant physicians as the process itself incurs an additional risk for patient survival. Rao et al. showed that the mortality risk increased significantly after kidney graft failure when compared with first-time kidney transplant candidates on the waiting list (hazard ratio 1.78, $p < 0.0001$), and mortality was greater among patients with DM than those without DM (hazard ratio 1.93 vs. 1.69) (113). Similar findings were present in type 1 DM kidney transplant patients who lost kidney graft and returned on dialysis (114).

These data suggest that it is advisable for diabetic kidney transplant patients with failing kidney grafts to be evaluated for retransplantation before they actually return to dialysis. Nonetheless, retransplantation does represent a significant challenge because of the increased risk of subsequent graft failure that has been documented (115,116). Additional studies are needed to define the best timing for a repeat transplantation, and the optimal management of diabetic patients undergoing repeat kidney transplantation.

Conclusion

Although kidney transplantation represents the best opportunity for diabetic patients with ESRD, improving their survival after kidney transplantation remains a substantial challenge. As diabetic patients, on dialysis or after kidney transplantation, continue to carry a huge

cardiovascular burden, only approaches that address multiple risks will have the potential to make an impact on outcomes. Neither improvement in glycemic control, improvement in hypertension and hyperlipidemia, prevention of weight gain, nor smoking cessation alone is likely going to change the outcome, but the combination of all of them will potentially help our patients to achieve a longer survival.

Since clinical trials assessing the cardiovascular benefit of particular therapeutic interventions in kidney transplant patients are scarce to nonexistent, future research in this area will be critical to guiding our approach. Until then, physicians must extrapolate the best evidence practice obtained from the general population to the diabetic kidney transplant population.

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