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Chronic Renal Failure after Transplantation of a Nonrenal Organ

Silas P. Norman and Akinlolu O. Ojo

Division of Nephrology, Department of Medicine, University of Michigan Medical School, Ann Arbor, Michigan, USA

Abstract

The expansion of nonrenal solid organ transplantation and the improved longevity of organ recipients have been accompanied by an increase in the number of recipients identified with chronic kidney disease. The most important risk factor for posttransplant chronic renal dysfunction is the baseline renal function at the time of transplantation, and the dominant etiologic factor in the posttransplant period is acute and chronic nephrotoxicity due to calcineurin inhibitors (cyclosporine and tacrolimus). Nonrenal organ transplant candidates arrive with a high burden of chronic kidney disease risk factors and significant preexisting kidney disease, which are worsened by transplant-related factors: (i) long-term exposure to the acute and chronic nephrotoxic effects of drugs, and (ii) episodic acute kidney injury due to the hemodynamic perturbations attendant to the transplantation procedure and posttransplant intercurrent illnesses. Normative values of serum creatinine opacifies significant pretransplant kidney disease, leading to significant underestimation of the burden and severity of kidney disease, with consequent failure to implement preventative strategies early. The reported prevalence of chronic kidney disease varies by organ and definition of chronic kidney disease applied. Overall, significant chronic impairment in kidney function is evident in 50-85% of heart, liver, and lung recipients within four years after transplantation. The risk of end-stage renal disease requiring maintenance dialysis or kidney transplantation averages 2-3% per year. Studies show that advanced chronic kidney disease and end-stage renal disease confers a 3-4-fold increased risk of mortality in affected recipients. Clinical management of posttransplant chronic kidney disease principally entails minimization of calcineurin inhibitors and substitution with other agents such as sirolimus and mycophenolate mofetil. The initial studies of calcineurin inhibitor minimization or discontinuation, while typically associated with modest improvement in renal function, have not shown extended preservation of renal function and may be associated with acute organ rejection. There are no specific therapies for preserving renal function in nonrenal organ recipients, but experimental studies suggest that alpha-melanocyte stimulating hormone and anti-transforming growth factor monoclonal antibodies may abrogate the nephrotoxic effects of calcineurin inhibitors. **(Trends in Transplant. 2009;3:59-69)**

Corresponding author: Akinlolu O. Ojo, aojo@umich.edu

Correspondence to:
Akinlolu O. Ojo
University of Michigan Medical Center
Division of Nephrology
3914 Taubman Center, Box 5364
Ann Arbor, MI 48109-5364, USA
E-mail: aojo@umich.edu

Key words

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Introduction

End-stage organ failure and chronic kidney disease (CKD) both share multiple traditional risk factors such as hypertension, diabetes mellitus, and chronic glomerular ischemia due to poor renal perfusion. Hence, patients who present as candidates for heart, liver, or lung transplantation have a high prevalence of CKD. The high burden of preexisting kidney disease in solid organ transplant candidates is made worse by transplant-related factors such as long-term exposure to nephrotoxic drugs, principally calcineurin inhibitors (CNI), and episodic acute kidney injury (AKI) due to the hemodynamic perturbations attendant to the transplantation procedure and posttransplant intercurrent illnesses. Cumulatively, recurrent AKI and progressive posttransplant CKD potentiate cardiovascular disease, aggravate metabolic risk factors, increase allograft dysfunction, and lead to premature mortality. In this review, the epidemiology and pathogenesis of kidney disease in nonrenal organ transplant recipients (heart, liver, lung, and their combinations) are discussed, global and organ-specific risk factors for CKD are described, and the therapeutic options for the prevention and management of kidney failure in nonrenal organ transplantation are critically appraised in the light of the paucity of level one evidence on the durability of the therapeutic benefits that can be expected from the widely utilized treatment options for posttransplant kidney dysfunction.

Epidemiology and risk factors

Growth in the rate of nonrenal organ transplantation is more rapid than the growth in kidney transplantation alone. The overall population of nonrenal organ transplant recipients is fast approaching that of kidney transplant recipients. In 2005, the number of individuals living with a nonrenal organ transplant in the USA was 70,073 compared to 97,558 individuals with a kidney only transplant[1]. The expansion of nonrenal solid organ transplantations and their improved longevity has been accompanied by an increase in the number of recipients identified with CKD[2-7]. The prevalence of CKD in nonrenal transplant recipients ranges in estimates from 5-90%[2,4,8-12]. The wide variability in prevalence estimates reflects the use of non-standardized definitions of CKD, differences in susceptibility across organ types, the mix of demographic groups, and the varying length of posttransplant intervals studied. Using a standardized CKD definition developed by the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (K/DOQI)[13] for stages 4 and 5 CKD (glomerular filtration rate, GFR, $\leq$ 29 ml/min/1.73 m^2), data from the U.S. Scientific Registry of Transplant Recipients (SRTR) found a cumulative incidence of CKD to be 8, 18.1, and 27% (liver recipients), 1.9, 10.9, and 21% (heart recipients), 2.9, 15.8, and 24% (lung recipients), at one, five, and 10 years posttransplantation, respectively[2]. Among all nonrenal transplant recipients, the estimated annual incidence of end-stage renal disease (ESRD) was 1.0-1.5%[2].

Predilection for CKD differs by organ type, with liver transplant recipients having the highest prevalence of CKD[6,14-17] compared to comparatively lower rates reported in the recipients of heart-lung transplants, although the latter are predominantly young recipients

with a mean age of 33 ± 15 years at the time of transplantation[18]. Older age at transplantation alone does not explain the higher predilection for CKD in liver recipients as their mean age at transplantation (44 ± 18 years) is comparable to that of heart-only transplant recipients (47 ± 18 years) who have a lower rate of CKD[18]. O'Riordan, et al. found a prevalence of 65.1% for stages 3-5 CKD at 10 years posttransplantation in liver transplant recipients. The rate of loss of kidney function and progression to ESRD follows a complex nonlinear pattern. Regardless of the baseline renal function, accelerated decay of GFR tends to occur within the first six months posttransplant, followed by a slower rate of decline interspersed by episodic and transient AKI, which can occur in up to 25% of recipients annually[19,20].

Predisposing factors for posttransplant CKD can be categorized into global risk factors common to all nonrenal organ transplant recipients, and organ-specific risk factors that have been found to increase risk in individual organ types. Table 1 depicts the two categories of risk factors[18,21-23]. The most commonly identified global risk factors include advancing age, pretransplant renal dysfunction, hypertension, diabetes mellitus, chronic hepatitis C virus (HCV) infection (as demonstrated by anti-HCV$^+$ antibody seropositivity), and female gender[2,23-26]. Interestingly, black race, a powerful risk factor for CKD in the general and kidney transplant populations, has not been identified as an independent predictor of posttransplant CKD in nonrenal organ transplant recipients. Although there appears to be a vintage effect in liver transplantation, in which transplantation prior to 1990 was a potent risk factor[2], a trend has not been consistently demonstrated. The most consistent risk factor for kidney dysfunction in the nonrenal organ transplant population is the level of renal function prior to transplantation. The mean GFR prior to transplantation is equivalent to stage 3 CKD in over 20% of candidates, with the majority of transplant candidates being at stage 2 CKD at the time of transplantation[2,25,27]. Although much of the CKD in nonrenal transplant recipients becomes clinically overt in the posttransplant period, disease is commonly the result of kidney injuries that predate transplantation[28-30], and most clinical studies have found a significantly high rate of pretransplant renal dysfunction, which tends to progress relentlessly after transplantation[31-36].

Pathogenesis of posttransplant chronic kidney disease

Pretransplant mechanisms

A number of pathogenetic mechanisms operate in concert and affect recipients differently, depending on the type of nonrenal transplantation being considered[37]. In end-stage liver disease (ESLD), hypotension is commonly present and the progressive disruption of abdominal blood flow that accompanies cirrhosis and hepatorenal syndrome often leads to substantial and protracted compromise of renal blood flow. Renal deposition of IgA molecular complexes in the kidneys of ESLD patients, partly due to a lack of hepatic clearance of the antibody, has been well documented[29,38]. Additionally, common causes of hepatic cirrhosis such as HCV (with or without cryoglobulinemia), and to a lesser extent hepatitis B virus (HBV) infections, also cause direct kidney injury[24,39]. Although infrequently performed, biopsy studies of liver disease patients revealed that substantial glomerular injury accompanied ESLD, even in the setting of normal serum creatinine concentrations. Crawford, et al. and McGuire, et al. independently found that > 80% of HCV-infected cirrhotic patients who had a kidney biopsy at the time of liver transplantation had evidence of an immune complex glomerulonephritis[30,39].

Cardiac transplant candidates frequently have atherosclerotic vascular disease[28]. As

Table 1. Global and organ-specific risk factors for chronic kidney disease in nonrenal organ transplant recipients[18,21-23]

Global risk factors	Organ-specific risk factors		
	Heart	Liver	Lung
Age at transplantation Female gender Systemic hypertension Diabetes mellitus Drug-induced nephrotoxicity (non-immunomodulating drugs) Preoperative renal function Perioperative acute renal failure Calcineurin inhibitors	Systemic atherosclerosis Renal hypoperfusion due to congestive heart failure Cyanotic congenital cardiac disease	Secondary IgA nephropathy Hepatitis B- or C-associated glomerulonephritis Hepatorenal syndrome Oxalosis Repeat liver transplantation	Cystic fibrosis Pulmonary hypertension Focal segmental glomerulosclerosis secondary to chronic hypoxia

systolic function deteriorates, increasing diuretic requirements and cardiorenal physiology may further decrease effective renal perfusion. As a result, the typical cardiac transplant candidates often experience ongoing renal ischemia and upregulation of the renin-angiotensin-aldosterone system (RAAS), despite total body volume overload, which further contributes to renal vasoconstriction and perioperative acute ischemic injury[40]. In lung transplant candidates, kidney injury may result from portal hypertension, atherosclerosis (in long-term smokers), and frequently indicated treatment with nephrotoxic anti-infective agents (e.g. aminoglycosides), along with renal dysfunction associated with the underlying primary cause of end-stage lung disease (e.g. cystic fibrosis-associated oxalosis, urolithiasis, and medullary calcinosis)[11,16,31,41]. Because a significant fraction of lung transplant candidates are relatively young at the time of transplantation (e.g. cystic fibrosis patients), there is a significantly long lifetime risk for the development of CKD in transplant survivors[42].

In each of the nonrenal transplants considered, the extent of kidney injury at the time of organ transplantation is often under appreciated. Chronic illness and the extent of muscle wasting, often masked by the edema, typically accompanies progression to end organ failure in liver and heart transplant candidates. Poor nutritional status and protein catabolism result in reduced creatinine generation. For these reasons, normative values of serum creatinine may obscure significant pretransplant kidney disease. Studies by Gonwa, et al., Delanaye, et al. and Broekroelofs, et al. revealed the limitations of creatinine-based estimations of renal function in liver, heart, and lung transplant recipients[27,43,44]. Creatinine-based estimations tend to suggest better renal function than gold standard I^{125} iothalamate studies in these patients[45]. Biopsy studies also show that most of the pretransplant renal injuries have a high chronicity index[46], such that posttransplant progression is inexorable with significant morbidity and mortality[47-49].

Surgical and perioperative acute renal failure

At the time of transplant surgery, AKI is common. Acute kidney injury, defined as a 25% increase in serum creatinine from baseline or an absolute rise in serum creatinine ≥ 0.5 mg/dl, occurs in up to 61% of liver, 60% of lung, and 30% of cardiac transplant recipients[5,50-54]. Acute kidney injury is the result of operative and perioperative hypotension, bleeding, diuretics, and the institution of calcineurin inhibition (cyclosporine, tacrolimus) during the transplant hospitalization[3]. Heart transplant recipients may also suffer kidney injury from vascular cross-clamping at the time of surgery. Much of the ischemic kidney injury in this setting is largely unavoidable, but

nonetheless contributes to the renal injury associated with transplant surgery. The risk for operative AKI is increased in patients with abnormal renal function at the time of transplantation[2,51,55-58]. A number of transplant recipients with AKI (up to 25, 15, and 10% of liver, heart, and lung, respectively)[59-62] require hemodialysis or continuous renal replacement therapy during the initial transplant hospitalization[55,63]. The need for renal replacement therapy following nonrenal organ transplantation is associated with future development of CKD as well as a doubling of one-year posttransplant mortality compared to recipients without AKI[55,59,61,62]. A subset of recipients who experience AKI at the time of organ transplantation may fail to recover renal function and require chronic dialysis. An additional source of renal insult is slow or poor function of the transplanted organ, which can continue to prolong ischemic renal injury[60,64]. Acute kidney injury, with or without the need for dialysis, is a strong risk factor for posttransplant CKD[2,55,62].

Posttransplant mechanisms

Many posttransplant events contribute to the overall burden of kidney disease in nonrenal transplant recipients[65-67]. A significant part of CKD development or progression results from ongoing renal insults that accumulate from the traditional CKD risk factors[68] (hypertension, new-onset diabetes after transplantation, and dyslipidemia are present in 65-90, 1-2, and 45-80%, respectively, of nonrenal transplant recipients)[69-72]. Chronic HCV infection has also been linked to new-onset diabetes after transplantation and an increased risk of CKD[73].

Renal injury is a well-established adverse effect of CNI and mammalian target of rapamycin (mTOR) analogs (sirolimus), which are two immunosuppressive drug classes commonly used in nonrenal organ tranplantation[74,75]. The nephrotoxic effects of these agents either alone or in combination are broad[10,76,77]. Calcineurin inhibitors are potent vasoconstrictors that profoundly affect both afferent glomerular blood flow and promotion of systemic hypertension[78,79]. Chronic CNI injury, clinically manifested by increased serum creatinine, subnephrotic range proteinuria, and a bland urine sediment, is present in the majority of long-surviving, nonrenal transplant recipients. Kidney biopsy studies demonstrate histologic changes consistent with long-term CNI nephrotoxicity in 60-70% of heart and liver transplant recipients with posttransplant ESRD[10,80].

The hemodynamic and nephrotoxic effects of CNI are mediated through inhibition of nitric oxide and alterations in the RAAS[40,81-83]. Angiotensin II (AtII) is a potent vasoconstrictor that promotes interstitial scarring in the kidney. Upregulation of AtII receptors has been demonstrated in patients exposed to cyclosporine, and serves as one mechanism of renal dysfunction[84,85]. Aldosterone increases sodium and water retention and, in the presence of AtII, also upregulates the expression of plasminogen activator inhibitor-1, which may directly lead to glomerular injury[81,86-92]. Calcineurin inhibitors also promote the activity of other profibrotic and thrombotic cytokines, such as platelet-derived growth factor, thromboxane, and transforming growth factor-beta 1 (TGFβ-1)[93,94]. The latter has been shown to cause interstitial renal scarring in murine models of kidney injury and likely plays a part in chronic allograft nephropathy seen in renal transplant recipients[95,96]. Among heart transplant recipients, individuals homozygous or heterozygous for TGFβ-1 codon 10 gene are 3-4-times more likely to develop CKD after CNI exposure than recipients not expressing the gene[97-99]. Increased intrarenal expression of additional profibrotic substances, such as collagen, fibronectin, osteopontin, and matrix metalloproteinases 2 and 9, have also been shown in patients exposed to CNI[94,100].

Calcineurin inhibitors also cause metabolic changes that can disturb kidney function. The CNI are diabetogenic and 5-20% of nonrenal transplant recipients may develop new-onset diabetes following transplantation[73,101]. Furthermore, the two currently available CNI formulations (cyclosporine and tacrolimus) lead to dyslipidemia, which in combination with hypertension has been shown to accelerate renal injury in the general population. Superimposed on CNI immunosuppression are often anti-infective and anti-inflammatory agents that may increase nephrotoxicity.

Sirolimus is increasingly used as part of the immunosuppressive regimen in nonrenal transplant recipients. Sirolimus promotes dyslipidemia, causes anemia, and has been associated with new-onset proteinuria[102,103]. When used in combination with CNI, sirolimus potentiates CNI-related renal toxicity[96,104,105]. Cyclosporine, tacrolimus, and sirolimus, through the promotion of hypertension, new-onset diabetes after transplantation, and dyslipidemia, may accelerate atherosclerosis which also negatively impacts renal function.

Potent immunosuppressive medication regimens that arrived in clinical transplantation in the 1990s have heightened the risk of infectious renal complications such as polyomavirus (BK) nephropathy[106-109]. Polyomavirus is trophic to the bladder epithelium and has been shown to cause nephropathy in heart transplant recipients[109].

Although long-term renal injury from CNI exposure appears to be the major histologic feature in nonrenal transplant recipients, such injury may be indistinguishable from unrelated, focal segmental glomerulosclerosis and chronic ischemia changes associated with atherosclerotic vascular disease[110]. *De novo* glomerular diseases have also been documented in nonrenal organ transplant populations[24,52,111,112].

Consequences of development of chronic kidney disease

The development of CKD following nonrenal organ transplantation is associated with increased morbidity and mortality[32,53,57,113-116]. Nonrenal transplant recipients with CKD experience increased hospitalizations, financial costs, and infections compared to recipients with normal renal function[33,117]. In addition, compromise of renal function can have a detrimental effect on the transplant organ, with worsening transplant function further negatively impacting kidney function in a vicious cycle[47,53,69]. Decreased renal function can affect recipient management by complicating medication interactions and forcing dose adjustment or exclusion of important and critically needed pharmacologic agents. Because serum creatinine GFR estimating equations tend to underestimate the severity of kidney dysfunction, recipients are at risk for inadvertent medication overexposures and toxicities.

A significant and growing minority of nonrenal transplant recipients with CKD progress to ESRD and, in this group, maintenance dialysis therapy is associated with substantially increased mortality[118-120]. Nonrenal transplant recipients on dialysis experience an increased mortality risk compared to non-transplant ESRD patients.

Prevention and management of posttransplant chronic kidney disease

Prior to transplantation, a precise estimate of kidney function should be obtained. An astute awareness of the potentially misleading GFR estimates based on serum creatinine is paramount, and GFR measurements should be obtained whenever possible[121,122]. When measured GFR is not feasible, as is more frequently the case, the modification of diet in renal disease equation has been suggested to be a

more accurate approximation of GFR compared to the other estimating equations[27]. Organ transplant candidates and recipients with evidence of renal dysfunction and those at increased risk of preoperative AKI and/or CKD should be referred early for nephrology consultation. In many instances, early involvement and coordination of care with nephrology can facilitate prompt diagnosis and preventative management to minimize acute kidney injury and/or mitigate the rate of progression of CKD[123].

Aggressive CKD management using established clinical guidelines may delay or avert the need for renal replacement therapy. Treatment of anemia, minimization of calcium and phosphorus abnormalities, correction of hyperkalemia and acidosis are important therapeutic steps that can reduce CKD morbidity and premature mortality[13]. Adjustment of the doses of medication consistent with the level of GFR and recognition of medication interactions that may exacerbate nephrotoxicity can also help to limit perioperative renal injury and decrease intercurrent episodes of AKI, which is very common and can itself contribute to diminished renal survival.

In the maintenance phase of nonrenal transplant recipient management, control of traditional and transplant-specific CKD risk factors can help to minimize CKD progression. Transplant-specific recommendations and the clinical guidelines developed for the general population are useful tools. Hypertension should be treated according to goals set forth in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of Hypertension (JNC-7)[124]. Increased utilization of RAAS blockade may decrease TGFβ levels and AtII-associated interstitial scaring[100]. Pre-transplant and new-onset diabetes mellitus along with hyperlipidemia should be controlled according to American Diabetes Association[125] and National Cholesterol Education Program Adult Treatment Panel III[126] guidelines. Smoking cessation, diet, and weight loss are non-pharmacologic steps that are uniformly helpful and may have salutary impact on the development and progression of CKD.

Calcineurin inhibitor minimization has been used as a strategy in the renal toxicity associated with long-term CNI exposure[127,128]. Substitution of CNI with mycophenolate mofetil may be beneficial in nonrenal transplant recipients[129,130]. Sirolimus also allows for CNI minimization, but reports of long-term allograft and renal benefit are mixed[131-134]. Early minimization of CNI appears to have a more significant impact on improving renal function than late withdrawal[129,130]. There is some evidence that tacrolimus may have a less deleterious effect on renal function than cyclosporine, but the improvements in renal function may not be clinically relevant[135-138]. Reduction of CNI may have additional benefits in the form of improved blood pressure control and reduction of dyslipidemia. Although CNI minimization, when possible, appears beneficial, *de novo* CNI avoidance appears to be associated with increased allograft rejection episodes and is not supported by high-quality clinical trial evidence of safety and efficacy[46,130,139].

Although there is no specific therapy for CNI-induced nephrotoxicity, two promising agents, alpha-melanocyte stimulating hormone (α-MSH) and anti-TGFβ antibody, have been showed to confer a renal-protective effect against CNI toxicity. Lees, et al.[140] showed that chronic CNI nephrotoxicity is partly mediated by Bax and Bcl2-related apoptosis pathways, and demonstrated that in male Sprague-Dawley rats fed with a low-sodium diet, 42 days of MSH infusion attenuated CNI-induced tubulointerstitial fibrosis and renal tubular cell apoptosis. In an experimental rodent model of heterotopic heart transplantation, Khanna, et al.[141] showed that TGFß partly mediates the immunosuppressive and nephrotoxic effects of cyclosporine, and 1 mg/kg body weight of anti-TGFß antibody inhibited the CNI-induced expression of fibrogenic molecules and reduced renal toxicity.

In patients with progressive renal dysfunction, early referral to nephrology is essential. Kidney transplantation remains the best option for many nonrenal transplant recipients requiring chronic renal replacement therapy[142]. As with transplant-naive candidates, preemptive transplantation and living donor kidney transplantation afford the best survival advantages over dialysis[143-145]. Previous nonrenal transplant recipients with ESRD appear to be waitlisted for a kidney transplant at a relatively high frequency (> 45% of ESRD nonrenal transplant candidates)[2]. Kidney transplantation has been shown to result in improved outcomes in selected heart, lung, and liver transplant recipients[5,111,146]. A registry study compared the survival benefit in nonrenal transplant recipients with ESRD receiving dialysis versus a kidney transplant and found that kidney transplantation in previous nonrenal transplant recipients was associated with a 44% reduction in long-term risk of death compared to remaining on the waiting list[2].

Summary and conclusions

Acute kidney injury and CKD are common and increasingly important consequences of successful nonrenal organ transplantation. Kidney disease confers significant excess morbidity and premature mortality in affected individuals. A high burden of unavoidable pretransplant renal disease and posttransplant intercurrent AKI contribute to diminished renal survival in nonrenal organ recipients. Liver transplant recipients appear to be at the highest risk of renal dysfunction. Early recognition of kidney impairment and referral for nephrology services may positively impact kidney outcomes. Durable improvement in renal function and delayed progression of CKD from CNI minimization and CNI withdrawal are intuitively attractive and widely utilized treatment options, but are not supported by robust clinical trial evidence. The timing of either CNI minimization or its complete avoidance that would preserve renal function without jeopardizing allograft viability is not known. In nonrenal transplant recipients with ESRD, kidney transplantation is associated with improved outcomes.

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