

Review Article

Cardiovascular Manifestations of Allograft Dysfunction in Renal Transplant Recipients: a Review

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Abstract

Introduction: Cardiovascular complications are the leading cause of death among renal transplant recipients; renal graft dysfunction has special effects on cardiovascular morbidity and mortality.

Review: Several studies have demonstrated a significant correlation between creatinine level and major coronary events, congestive heart failure and cerebrovascular events. Cardiovascular mortality has been related in different reports to serum creatinine levels and duration on renal replacement therapy. A low estimated glomerular filtration rate (eGFR) was also found to be a significant predictor of death in the pediatric kidney transplant population. Immunosuppressive therapy is also associated with several adverse effects. It has been shown that earlier withdrawal of steroids is associated with less cardiovascular effects, especially via reduction in the incidence of hypertension, hyperlipidemia, weight gain, and post-transplant diabetes. The introduction of calcineurin inhibitors (CNIs) has led to an increase in the number of renal transplant patients dying with a functioning graft, mainly because of cardiovascular disease. Compared to CNIs, mycophenolate mofetil has been proposed to reduce infiltration of circulating lymphocytes to the atherosclerotic plaque. Sirolimus is known to be associated with higher incidence of hyperlipidemia and hyperglycemia but lower incidence of hypertension.

Conclusion: Dialysis duration, renal allograft dysfunction and the immunosuppressive agents used enhance cardiovascular risk among the renal transplantation population. Transplanted children are at a particularly high risk of cardiovascular events post-transplantation.

Keywords: Kidney Transplant; Cardiovascular Events

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Introduction

Chronic kidney disease (CKD) affects several organs in the human body, among which the cardiovascular system is probably the most vulnerable with usually ominous effects [1, 2]. Evidence showed that most of the mortality associated with kidney diseases is due to cardiovascular events rather than the primary renal disease [3]. On the other hand, some reputable studies have demonstrated strong evidence that the incidence and outcomes of cardiovascular events directly correlate with kidney disease advancement, and vice versa [4, 5]. Hence one may assume that kidney transplantation may ameliorate the course of cardiovascular disease and its associated morbidity in CKD patients.

Renal transplantation is generally considered the treatment of choice for patients with end-stage renal disease (ESRD). It does not only improve the quality of life but also has considerable effects on patients' survival [6]. This survival advantage may be attributed to an improvement in cardiovascular health. On the other hand, renal allograft dysfunction may be associated with adverse effects on the cardiovascular system. In the current article, we aimed to review the literature on the effects of renal allograft dysfunction on cardiovascular related health status and on the short and long-term survival of kidney transplant recipients.

Cardiovascular events and renal graft dysfunction

Cardiovascular events are one of the most common morbidities in renal transplant recipients. This becomes even more relevant when we consider the high rate of

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Table 1: Studies investigating association between renal allograft function and cardiovascular mortality cal presentation of studied dense deposit disease (DDD) patients

Study	Main findings	Sample size
Weiner <i>et al</i> , 2012 [21]	At eGFR < 45 mL/min/1.73 m ² , each 5 mL/min/1.73m ² increase in eGFR was associated with a 15% lower risk of death (HR 0.85, 95% CI 0.8-0.9)	3676
Bahous <i>et al</i> , 2012 [23]	eGFR at inclusion was a strong and independent predictor of the composite recipient outcome	95
Soveri <i>et al</i> , 2012 [10]	Total mortality was associated with creatinine values (HR 1.005, 95% CI 1.003-1.007)	2102
Pilmore <i>et al</i> , 2010 [24]	Compared to lower eGFR values, eGFR >48 ml/min/1.73m ² was associated with a significantly lower cardiovascular death rate (HR 0.66, 95% CI 0.45-0.95) in the Australia/ New Zealand registries	
Koshy <i>et al</i> , 2009 [25]	Low eGFR at one year post-transplant was significantly associated with increased risk of death among pediatric patients	274
Vanrenterghem <i>et al</i> , 2008 [15]	The risk of all-cause death was increased in renal recipients with higher serum creatinine levels (HR 1.298, 95% CI 1.048-1.608) in patients with one year functioning grafts	2071
Jardine <i>et al</i> , 2005 [26]	Increments of 1 mg/dL in creatinine level are associated with increased cardiac death (HR 2.65, P <0.0001) in patients with six months functioning grafts	1052
Fellström <i>et al</i> , 2005 [13, 14]	Elevated serum creatinine is a significant risk factor for cardiac death in both univariate (HR 2.29, 95% CI 1.58-3.32) and multivariate (HR 2.94, 95% CI 2.01-4.31) analyses	2102
Meier-Kriesche <i>et al</i> , 2003 [27]	With a reference serum creatinine value of 1.5 mg/dL, higher levels were significantly associated with cardiovascular death: 1.5–1.6 mg/dL (HR 1.19, 95% CI 1.02–1.3), 1.7–1.8 mg/dL (HR 1.37, 95% CI 1.16–1.62), 1.9–2.1 mg/dL (HR 1.49, 95% CI 1.25–1.76), 2.2–2.5 mg/dL (HR 1.67, 95% CI 1.38–3.03) and 2.6–4.0 mg/dL (HR 2.26, 95% CI 1.85–2.75)	58900

mortality associated with cardiovascular events among kidney transplant recipients, which is 10-20 times higher than the general population [7]. Matas *et al* showed that the major cause of death among renal allograft recipients with a functioning graft for at least 10 years was cardiovascular events, but did not correlate the mortality rate with allograft function [8]. Impairment of kidney function is a known predictor of cardiovascular events in the non-transplant population. Even a mild reduction in glomerular filtration rate (GFR) predicts increased cardiovascular events [9]. However, there is limited data on the relevance of kidney graft dysfunction to the rate of cardiovascular events post kidney transplantation.

In a recent study, Soveri *et al* showed that major adverse cardiac events could be predicted using a seven-variable model that includes age, previous coronary heart disease, diabetes, low-density lipoprotein level, creatinine level, number of kidney transplants, and smoking [10]. The hazard ratio (HR) of major adverse cardiac events for each 0.2 mg/dL increment in serum creatinine level was 1.005 (95% CI 1.003-1.007). Israni *et al* evaluated

a group of kidney transplant recipients 1-5 years after kidney transplant and reported significantly higher rates of coronary events at three years for patients with eGFR 40-50 mL/min (HR 1.18, 95% CI 0.98–1.42) and for eGFR <40 mL/min (HR 1.46, 95% CI 1.23–1.72). Delayed graft function was also associated with coronary heart disease (HR 1.22, 95% CI 0.99–1.50) [11]. Abbot *et al* compared renal transplant recipients with eGFR >69.7 mL/min/1.73m² with those having eGFR <44.8 mL/min/1.73m² and found that patients in the latter group are at a higher risk of acute coronary syndrome (HR 2.16, 95% CI 1.39-3.35) and congestive heart failure (HR 2.95, 95% CI 2.24-3.9) [12]. Fellström *et al* meticulously observed a group of kidney transplant recipients and reported that for each 1.1 mg/dL increase in serum creatinine values, renal transplant recipients would be at higher risk of developing major adverse cardiac events (HR 1.63, 95% CI 1.23–2.17) but no change in the risk of developing non-fatal myocardial infarction (HR 1.12, 95% CI 0.69–1.82) or stroke (HR 1.30, 95% CI 0.75–2.25) [13,14].

On the other hand, Vanrenterghem *et al* followed 2071 kidney transplant recipients with functioning grafts for more than one year and found no statistically significant correlation between serum creatinine values and the incidence of cardiovascular events [15]. de Mattos *et al* also found no significant relation between serum creatinine values and cardiac events, but a serum creatinine value of more than 1.6 mg/dL was a significant risk factor for cerebrovascular events (HR 3.16, 95% CI 1.59-6.3) [16].

Cardiovascular mortality and renal allograft function

Among the non-transplant population, it has been demonstrated that even minor impairment in kidney function is associated with increased incidence of cardiovascular mortality [17-19]. In kidney transplant context, the quality and rate of decline in kidney allograft function have also been significantly related to cardiovascular mortality [11, 20]. Weiner *et al*, showed that an eGFR <45 mL/min/1.73m² among kidney transplant recipients was associated with increased cardiovascular disease and death [21]. A second study from Sweden demonstrated that cardiovascular mortality among kidney transplant recipients was related to serum creatinine levels and duration on renal replacement therapy [10]. Furthermore, a study that included 1206 kidney transplant recipients on follow-up for 10 years found that high cardiac troponin-T levels (cTnT) were independently associated with patients' survival, irrespective of the cause of death [22]. They also demonstrated that patients with delayed kidney graft function and those having eGFR less than 30 mL/min/1.73m² at three weeks post-transplant were more likely to have elevated cTnT levels and thus remained at high risk.

Cardiovascular events and time on dialysis

A longer waiting time on dialysis is a well-known predictor of all-cause mortality among patients with functioning graft [28, 29], and this association is more significant among patients who had been on dialysis for one year at least [30, 31]. de Mattos *et al* reported that a history of more than one year on dialysis but no delayed graft function is associated with increased cardiac events post transplantation (HR 1.79, 95% CI 1.15-2.80) [16]. Abbot *et al* reported that among renal transplant recipients, patients with 1-1.79, 1.79-2.98 and more than 2.98 years of prior dialysis had higher rates of congestive heart failure, (HR 1: 2.34, 95% CI 1.80-4.67; HR 2.88, 95% CI 2.39-6.67 and HR 2.95, 95% CI 2.06-7.07 respectively) when compared to those with less than one year dialysis duration [12].

Still, controversial reports suggesting no role for pre-transplant dialysis duration on the patients' survival do exist [32]. Overall, data on the causative effects of pre-transplant dialysis duration on patients' survival remains scarce. More research addressing this critical issue is required.

Children

Cardiovascular events had been proposed as the leading [33] or the second cause of death in pediatric renal transplant recipients [34]. Proposed risk factors for cardiovascular diseases in pediatric kidney transplant recipients include renal graft insufficiency, hyperlipidemia, hyperhomocysteinemia, inflammation, malnutrition, anemia, and insulin resistance [35]. Despite strong evidence suggesting risk factors for cardiovascular disease development after pediatric renal transplantation, only few studies have attended the issue in pediatric kidney transplantation setting.

Renal transplantation has several cardiovascular advantages over dialysis therapy in ESRD children. It has been shown that kidney transplantation in children significantly decreases the left ventricular mass (LVM), and this decrease is progressive over time [36], while in pediatric kidney disease patients, LVM increases progressively [37]. Bilginer *et al* investigated several potential risk factors in pediatric renal allograft recipients and their possible relation to carotid intima-media thickness and, after multivariable adjustments, they found that the only significant risk factors were duration of CKD and duration of dialysis prior to transplantation, but not serum creatinine levels [38]. Due to the very early effects of renal dysfunction and uremia on carotid intima-media thickness in children and its association with pre-transplant dialysis duration [39], the general recommendation in children with kidney disease is to go for pre-emptive renal transplantation. In a population-based retrospective cohort study, Koshy *et al* followed 274 pediatric renal transplant patients with or without a functioning graft for median time duration of 11.9 years, and reported 13 (28%) cardiovascular deaths and 20 non-fatal cardiovascular events during 3037 patient-years of follow up [25]. A low eGFR was found to be a significant predictor of death in the pediatric kidney transplant population [25]. Putting these data together, we conclude that pediatric kidney disease patients should preferably receive pre-emptive renal transplantation with the shortest possible waiting time.

Immunosuppression and cardiovascular risk

Immunosuppressive therapy prevents graft rejection but is associated with several adverse effects. In the context of cardiovascular disease, corticosteroids are most commonly accused of increasing patients morbidity and mortality due to cardiovascular events. Corticosteroids are known to increase the risk of glucose metabolism disorders [40], induce endothelial dysfunction, hypertension, hyperlipidemia, and impair fibrinolysis. Withdrawal of corticosteroid, on the other hand, reduces the incidence of these metabolic disorders and post-transplantation diabetes [40]. Moreover, it has been shown that earlier withdrawal of steroids is associated with less cardiovascular effects, especially via reduction in the incidence of hypertension, hyperlipidemia, weight gain, and post-transplant diabetes [41]. Controversial findings were reported by Vincenti *et al* that early withdrawal of corticosteroids had no significant effect on the incidence of post-transplant diabetes, though it reduced the need for hypoglycemic agents [42]. The same observation was reported among the pediatric kidney transplant population [43].

The introduction of calcineurin inhibitors (CNIs) in the early 1980s had substantially decreased the rate of rejection episodes and improved allograft survival. However, the nephrotoxicity and hyperlipidemia associated with the use of CNIs led to an increase in the number of renal transplant patients dying with a functioning graft, mainly because of cardiovascular disease [44]. On the other hand, early discontinuation of CNIs had been associated with renal allograft dysfunction, increased incidence of acute rejections and kidney graft loss [45], so it is not an open road ahead. However, minimizing the dose of CNIs together with early withdrawal of corticosteroid therapy has been associated with decreased cardiovascular risk and improved patient survival without compromising allograft function [41]. Among CNIs, tacrolimus was shown to have better effect on allograft function compared to cyclosporine despite its greater impact on the cardiovascular system [46].

Mycophenolate mofetil (MMF) is a non-competitive inhibitor of inosine monophosphate dehydrogenase that applies cytostatic effects, particularly on proliferating T-lymphocytes. It had been very successful in reducing allograft rejection rates and improving outcomes in transplant populations. Wong *et al* found that MMF induces less inflammation, defined by CRP levels, than other immunosuppressive therapies [47]. Moreover, compared to cyclosporine and tacrolimus, MMF treatment has been proposed to reduce infiltration of circulating

lymphocytes to the atherosclerotic plaque [48,49]. The nephrotoxicity of MMF is less than that of CNIs; data on the incidence of MMF allograft nephrotoxic effects is limited and need more investigations.

Sirolimus is a mammalian target of rapamycin (mTOR) inhibitor known to be less nephrotoxic than the CNIs [50]. In clinical trials of early and late CNIs withdrawal, sirolimus resulted in improvement in renal function and blood pressure, with a trend to superior graft survival [51-54]. It is used as a substitute to CNIs to minimize the risk of nephrotoxicity in renal allograft recipients [51]. Regarding cardiovascular risk, compared to CNIs and corticosteroids which are mostly associated with hypertension, hyperlipidemia and hyperglycemia [55], sirolimus is known to be associated with higher incidence of hyperlipidemia and hyperglycemia [56]. This clinical data suggest the relevance of sirolimus therapy in reducing cardiovascular risk among renal transplant recipients.

Conclusion

Cardiovascular diseases are known serious complications following renal transplantation. Several factors are known to enhance cardiovascular risk among this population. These include dialysis duration, renal allograft dysfunction and the immunosuppressive agents used.

In children with advanced kidney disease pre-emptive renal transplantation is highly recommended. However, transplanted children are at a particularly high risk of cardiovascular events post-transplantation.

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