Review Article

Cardiovascular complication after kidney transplantation

Abstract:

Patient mortality after kidney transplantation continues to be a major clinical challenge, with approximately 1 in 5 recipients dying within 10 years of engraftment. Cardiovascular disease (CVD) is the most common cause of death after the 1-year posttransplant and it has been estimated that the risk of cardiovascular events is 50-fold higher than in the general population. Because of this, post transplant outcomes are substantially influenced by cardiovascular disease. The presence of both traditional and non-traditional risk factors contributes to this overwhelming burden of cardiovascular disease in patients with chronic kidney disease (CKD).

Introduction:

Patient mortality after kidney transplantation continues to be a major clinical challenge, with approximately 1 in 5 recipients dying within 10 years of engraftment [1]. Cardiovascular disease (CVD) is the most common cause of death after the 1-year posttransplant [2] and it has been estimated that the risk of cardiovascular events is 50-fold higher than in the general population [3]. Because of this, post transplant outcomes are substantially influenced by cardiovascular disease [4]. The presence of both traditional and non-traditional risk factors contributes to this overwhelming burden of cardiovascular disease in patients with chronic kidney disease (CKD)[5].

Atherosclerotic cardiovascular disease before kidney transplantation is three to four times more prevalent in the End Stage Renal Disease(ESRD) compared to the general population and has been shown to be the single most important predictor of cardiovascular mortality after transplantation [6]. In a cohort of more than 2000 primary allograft recipients, the incidence of cardiovascular events increased over time. Within 15 years of transplantation,

only 47% of surviving patients had not experienced any cardiovascular events [7]. Risk factors associated with cardiovascular complications were male gender, age, hypertension (HTN) before transplantation, longer duration of pretransplantation dialysis, cardiovascular event before transplantation, older era of transplantation, center-specific effect, posttransplant diabetes mellitus, increased pulse pressure after transplantation, use of corticosteroids and azathioprine, lower serum albumin after transplantation, and higher serum triglyceride levels after transplantation. The risk of death was also increased in patients with low or elevated hematocrit, while it was minimal with values of about 38% [7].

In spite of those issues, kidney transplantation has repeatedly been shown to reduce cardiovascular and all-cause mortality compared to dialysis. In renal transplant recipients, although cardiovascular mortality decreases after transplantation, the annual cardiovascular mortality still remained twofold higher than the general population and myocardial infarction is most common in elderly and diabetic patients [8]. Similarly, renal transplant recipients may have reduced risk of cerebrovascular events, and the risk of approximately 1% year incidence is still high compared to the general population [9, 10]. The elevated risk is attributed to both traditional risk factors such as hypertension, dyslipidemia, diabetes [11], and nontraditional risk factors such as immunosuppression, anemia, inflammation, and proteinuria [12, 13].

1. General background for nontraditional Risk Factors

Several studies indicate that post-transplant CVD events are related to the exacerbation of pre-transplant risk factors [14]. Before transplant, patients with CKD and ESRD are at

significantly increased risk for CVD events and hospitalization [15]. Careful selection of transplant candidates from this population imply that the post-kidney transplant population would have low rates of CVD events [16]. Certainly, early post-transplant events may be related to pretransplant risk factors, but later events may be more intrinsically related to decline in allograft function. Clinically, as kidney allograft function declines, post-transplant patients develop CKD, and are greater risk of mortality from CVD events as they approach ESRD [17, 18]. This is likely related to accelerated atherosclerosis, the occurrence of post-transplant diabetes, and other factors[19].

In a recent large cohort study by Bangalore et al [20] it was found that in patients with coronary artery disease, body-weight fluctuation was associated with a significant increase in the risk of cardiovascular events and death. The magnitude of this risk increased with greater variability in body weight and among those who were overweight or obese at baseline and was independent of traditional factors related to cardiovascular risk.

Table 1. Transplant-Specific Cardiovascular Risk Factors

Older age
Male
Caucasian
History of DM pre-transplant or PTDM
History of cancer
Cardiovascular comorbid conditions pre-transplantation
(History of myocardial infarction (MI), coronary revascularization,

congestive heart failure (CHF), a cerebrovascular event, or peripheral vascular disease (PVD))
Deceased donor transplantation
Body mass index (BMI) >30 kg/m^2
Years from ESRD to transplantation
Delayed graft function (DGF)
Panel-reactive antibody (PRA) titer at transplant >10%
Acute rejection
Post-transplant lymphoproliferative disease (PTLD)
Low GFR post-transplantation

GFR: glomerular filtration rate

2. Hypertension

Hypertension (HTN) is known to be a traditional risk factor for atherosclerosis which leads to premature allograft failure and death [21]. The prevalence of hypertension is approximately 70% in the kidney transplant population [22]. HTN after transplantation is associated with numerous factors that include pretransplantation HTN, cause of primary disease, and posttransplantation factors such as delayed graft function, immunosuppression therapy, rejection, transplant renal artery stenosis, acquired glomerular filtration rate (GFR), chronic immune and nonimmune injury, recurrent or de novo allograft glomerulonephritis, and weight gain. HTN is a risk factor for premature allograft failure, atherosclerosis, and death with a functioning graft [22, 23].

The calcineurin inhibitors (CIs) are known to disrupt the normal balance between endogenous vasodilators and vasoconstrictors leading to afferent arteriolar vasoconstriction and thus HTN. In part, this effect is mediated via activation of the sympathetic nervous system [24, 25] and also increased expression of endothelin [26]. The pathogenic role of

endothelin in this setting was described in this setting by administering an endothelin receptor antagonist that blunted the rise in blood pressure induced by cyclosporin A (CsA) in vivo [27]. Vasoconstriction is compounded by depressed nitric oxide induced vasodilatory activity [28]. A recent report described a novel mechanism by which CsA causes sodium retention in the thick ascending limb of the loop of Henle leading to HTN [29]. Moreover, Chiasson et al, recently showed that cyclosporine and tacrolimus alter T-cell subsets which can cause hypertension, vascular dysfunction and renal toxicity [30].

Steroids also elevate blood pressure via mineralocorticoid induced sodium retention. The effects are dose related, and the relatively low doses of steroids currently used after the first 6 to 12 months are thought to have a minimal impact on blood pressure. Patients with preexisting HTN appear to be more susceptible to this adverse effect of chronic steroid use [31]. Steroids are associated with multiple complications including hypertension, obesity, glucose intolerance, osteoporosis, avascular necrosis, glaucoma, cataracts, myopathy, and neuropsychiatric complications after transplantation[32]. In various older studies, steroid withdrawal was shown to improve blood pressure, glycemic control, and lipid profiles[33-35]. In truth, although steroid avoidance or early steroid withdrawal are now routinely practiced by many centers in the United States, there is no data that indicates such a practice has any beneficial impact on patient or graft survival [36, 37]. Furthermore, such practices have been shown to increase the early rejection rate which may adversely impact long-term graft function in at least some patients groups [38, 39].

3. Dyslipidemia

Immunosupressive drugs can adversely impact dyslipidemia. The prevalence of high cholesterol and hypertriglyceridemia is 35% after transplant. A recent study showed that

cholesterol efflux capacity is not an independent predictor of overall or cardiovascular mortality in renal transplant recipients [40]. However, the nature of cardiovascular disease in renal transplantation is not well defined and might differ from the general population [41]. Such a concept is supported, as we mentioned previously, by traditional risk factors not consistently being the major determinants of cardiovascular events in renal transplant recipients [42]. Although myocardial infarction due to obstructive coronary artery disease, the principal type of cardiovascular disease in the general population, is not uncommon in renal transplant recipients, increased cardiovascular mortality among renal transplant patients might be also attributable to an excess prevalence of sudden cardiac death and heart failure. Moreover, as kidney function declines, renal transplant recipients may develop uremia, which can cause uremic cardiomyopathy.

Because cardiovascular disease is so prevalent in kidney transplant recipients, it is reasonable to consider the kidney transplantation state to be a "coronary heart disease risk equivalent" when applying guidelines [43, 44]. This implies targeting plasma LDL cholesterol to less than 100mg/dl via a combination of therapeutic lifestyle changes and drug therapy. Changing immunotherapy may also impact dyslipidemia in a beneficial matter. For example, switching to tacrolimus from sirolimus or cyclosporine and withdrawing steroids may permit normalization of lipid levels without any other pharmacological intervention.

Statins are the lipid-lowering drugs of choice in transplant recipients. Holdaas, et al previously published his investigation of the use of Fluvastatin in kidney transplant recipients (Assessment of Lescol in Kidney Transplantation [ALERT]) which demonstrated efficacy in lowering cholesterol levels [45]. More importantly, cardiac deaths and nonfatal myocardial

infarcts, although not overall mortality, were also significantly reduced after a mean of 6.7 years of follow-up. Of note, earlier reports of this study that failed to demonstrate use in reducing cardiovascular events should remind the reader that most statin trials reveal divergent outcomes only after 5 or more years of follow-up.

It important to note that statin metabolism is at least partly inhibited by CI therapy which can lead to elevated blood and tissue concentrations with risk of adverse effects such as rhabdomyolysis. Consequently, it is recommended statins be used at reduced doses in cyclosporine treated transplant recipients. This interaction is further enhanced, if additional inhibitors of cytochrome P-450, such as diltiazem, are administered. Other measures that are often considered in order to minimize the risk of toxicity include the use of Pravastatin or Fluvastatin (which appear to have the least interaction with CIs), avoidance of other inhibitors of the cytochrome P-450 system, avoidance of fibrates, and periodic checking of plasma creatine kinase and liver function tests are also advisable [46]. Early reports that indicated that Pravastatin may reduce the risk of rejection in kidney and heart transplant recipients are probably of less relevance in the current era of "modern" immunosuppression[47, 48]. Rarely, nonstatin drugs are used to lower plasma lipids in transplant patients. Bile acid sequestrants, if used, should be taken separately from CI as they impair absorption of these drugs. Fibrates should be prescribed with extreme caution to patients on statins and CI.

4. New Onset Diabetes After Transplantation

Diabetes mellitus (DM) has become one of the most prevalent diseases in the United States with dire health and economic consequences[49]. Over the last decade, there have been improvements in the management of DM and cardiovascular disease. Likely reflecting these trends, recent studies have shown that since the mid-1990s there have been significant improvements in DM patient survival in the general population [50, 51]. The survival of patients with DM is in part compromised by an increase in cardiovascular (CV) risk. However, other variables contribute to the survival disadvantage of these patients [52]. For this reason, it has been difficult to pinpoint specific parameters that may explain the improving survival of patients with DM [50].

Diabetic nephropathy accounts for a large proportion of patients with end-stage renal disease[53-55]. Unfortunately, the outcomes of patients with DM treated with dialysis or kidney transplantation remain inferior to those of patients without DM [54, 55]. As in the general population, differences in posttransplant survival between recipients with and without DM are primarily due to higher CV- and infection-related deaths[52, 54]. Previous studies suggested that the survival of patients with DM after transplantation can be largely attributable to pretransplant variables[6, 54]. If that is the case one would expect that improvements in DM patient survival in the general population would translate into improvements in survival after transplant[49].

The incidence of new onset diabetes after transplant (NODAT) ranges from 2% to 53%[56, 57]. Risk factors include obesity, weight gain, hepatitis C, steroids, Tacrolimus, and restoration of insulin metabolism by the kidney allograft [58]. For reasons that remain

unclear, autosomal dominant polycystic kidney disease (ADPKD) is also a risk factor for NODAT[59]. In general, the causative pathophysiological mechanisms underlying new onset DM after transplantation include a decrease in the number and binding affinity of insulin receptors, malabsorption of glucose in peripheral organs, and activation of the glucose/fatty acid pathway. Such mechanisms appear particularly important in those with significant posttransplantation weight gain [60].

A novel risk factor for NODAT, hypomagnesemia, was reported in a retrospective series of 948 recipients[61]. A serum magnesium <0.74 mmol/L (1.8 mg/dl) was significantly a ssociated with increased risk of NODAT in baseline (HR1.58, 95% CI 1.07-2.34; P=0.0 2), time-varying (HR1.78, 95% CI 1.29-2.45; P<0.001), and rolling-average models (HR1. 83, 95% CI 1.30-2.57; P=0.001). Interventional trials are ongoing to determine if this as sociation can be remedied with magnesium supplementation (see section below on hypo magnesemia). Finally, an ongoing concern is the role of chronic corticosteroids in the d evelopment of NODAT. In a recent report stemming from a 5-year double-blind study comparing early corticosteroid withdrawal (CSWD) versus corticosteroid maintenance tap ered to 5mg/d (CCS) from 6 months onward, no difference in PTDM rates were noted (36.3% of CCS patients versus 35.9% of CSWD patients were diagnosed with PTDM by 5 years, although insulin therapy was more prevalent in the CCS cohort versus CSWD, 11.6% vs. 3.7%; p = 0.049)[62]. Thus, traditional risk factors (obesity) and nontraditiona l risk factors (hypomagnesemia) may help predict PTDM, while immunosuppression-relat ed risk factors (low-dose corticosteroids, tacrolimus dose/trough concentrations) may be l ess valuable.

5. Obesity

While obesity is not a traditional cardiovascular risk factor, its association with post transplant diabetes and its frequent consideration for transplant candidacy justifies discussion as a separate cardiovascular risk factor in kidney transplantation. Recently published trials continue to demonstrate the survival advantage of transplantation versus remaining on dialysis in obese candidates, but with greater clarity regarding risks. Using the UK renal and transplant registry data from 2004-2010, 1- and 5-year survival following transplant was superior to waitlisted candidates in all BMI subgroups, including BMI 35-40 and >40 kg/m^2 [63]. Further comparisons of obese to non-obese transplant recipients (BMI 18.5-25 kg/m^2) showed no differences in mortality with increasing BMI. However, conclusions regarding the latter subgroups are difficult to extrapolate as only 540 of the 13,526 total patients available for analysis had BMI >35 kg/m^2. Using statistical methodology to control for the competing risk of death, a United States registry analysis of 108,654 primary kidney transplant recipients from 2001-2009 demonstrated worse graft survival with increasing BMI [64]. With BMI 18.5-25 kg/m^2 as the reference, the subhazards ratios (SHRs) were: 30-35 kg/m^2= 1.15; p <0.001; 35-40 kg/m^2 = 1.21; p < 0.001; > 40 kg/m^2= 1.13; p = 0.002. A meta-analysis that did not account for the competing risk of death similarly found an increased risk of death-censored graft loss (HR = 1.06, 95% CI = 1.01– 1.12), an increased likelihood of delayed graft function (OR = 1.68, 95% CI 1.39– 2.03), and no significant difference in mortality risk in obese recipients (defined as BMI ≥30 kg/m^2) (HR = 1.24, 95% CI 0.90– 1.70).[65] Taken together, kidney transplant can be considered effective therapy from the obese patient's perspective compared to

dialysis, but with higher risks of morbidity (delayed graft function and graft loss) than nonobese transplant recipients that transplant programs must reconcile.

This additive risk noted in obese patients has prompted transplant centers to explore surgical options to optimize outcomes. In one series, laparoscopic sleeve gastrectomy was performed in 52 renal transplant candidates with a mean BMI of 43.0 kg/m^2 (range 35.8-67.7 kg/m^2), with 29 achieving goal BMI of < 35 kg/m^2 at a mean of 92 days (range 13-420 days) and 6 undergoing successful transplant.[66] A single-center series described minimally invasive robotic surgery in 67 living donor kidney transplants for patients with BMI ≥40 kg/m^2, employed to minimize the substantial risk of wound complications known to occur in this population.[67] There were no graft losses due to graft thrombosis or infection. The authors compared their outcomes with registry data (a total of 612 living donor transplants in recipients with BMI ≥40 kg/m^2 were performed during the period 2009-2014) and found similar rates of delayed graft function and equivalent graft function and patient survival, but 2% of morbidly obese recipients who underwent the open technique had graft loss due to infection or graft thrombosis. Perhaps expansion of these surgical approaches will lead to a greater comfort in evaluating and transplanting the obese transplant candidate.

6. Posttransplantation Anemia

Immediately after transplantation, pre-existing anemia is generally aggravated by perioperative blood loss compounded by myelosuppressive induction immunotherapy. Hemoglobin (Hgb) is expected to reach a normal level as time passes via normal production

of erythropoietin by the engrafted kidney [7]. However, a large number of renal allograft recipients remain anemic. As only one kidney is transplanted, kidney function seems to be only partially restored, resulting in an incomplete correction of anemia. This post-transplantation anemia (PTA) likely contributes to graft loss [68] or post-transplantation cardiovascular events, which are the second most common reason for allograft loss and the most common cause of death in patients with a functioning allograft. Persistent anemia after renal transplantation leads to decreases in mental capacity and quality of life.

Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) exacerbate or induce anemia in the transplant patient although for reasons that are incompletely understood[69]. In the TRESAM study, data from 4263 patients from 72 transplant centers in Europe was collected 6 months to 5 years posttransplantation [70]. The mean Hb levels before transplantation were significantly higher in the more recently transplanted recipients. At enrollment, 39% of patients were found to be anemic. Of the 8.5% of patients who were considered severely anemic, only 18% were treated with recombinant human erythropoietin (rHuEpo). Anemia was associated with impaired kidney function and use of azathioprine, ACE inhibitors, and ARB therapy.

Recombinant human erythropoietin is often administered to patients with CKD and more frequently to patients on dialysis. The use of rHuEpo after kidney transplantation remains to be defined. Van Biesen and associates reported the results of a trial in which patients were randomized to either receive rHuEpo three times a week immediately after transplantation or not. The time to reach a Hb level greater than 12.5 g/dl was 66 days in the rHuEpo group compared to 57 days in the control group. The authors concluded that while the

administration of rHuEpo reduced the duration of anemia, this effect was marginal, and the doses needed were high [71]. There was no difference in harder endpoints such as length of stay or patient or graft survival between the groups.

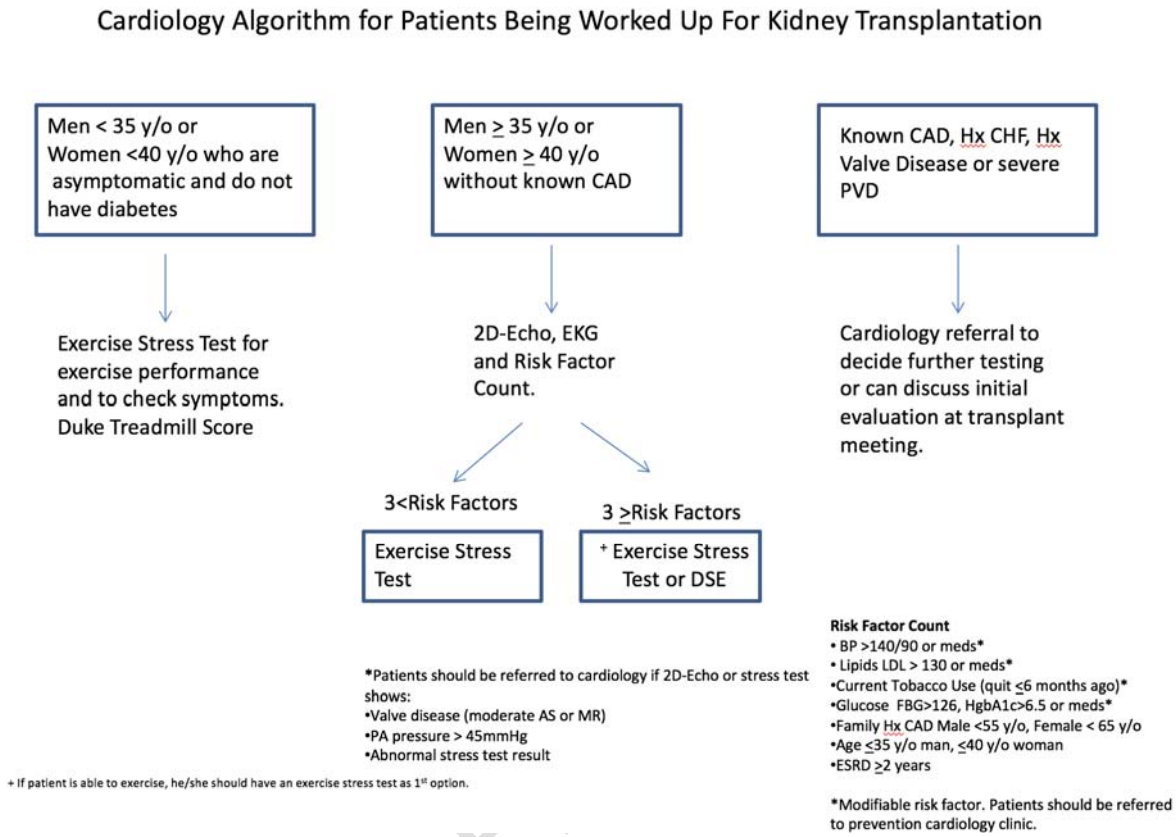
7. Evaluation of Atherosclerotic Cardiovascular Disease before Transplantation

Screening for atherosclerotic disease remains an important part of the transplant evaluation prior to surgery. Cardiovascular testing is generally recommended prior to listing and subsequently, in most patients, periodically. Below is an example of the algorithm that is used to evaluate and reevaluate patients in the kidney transplant wait list.

Conclusion: Post transplant outcomes are substantially influenced by cardiovascular disease. The presence of both traditional and non-traditional risk factors contributes to this overwhelming burden of cardiovascular disease in patients with chronic kidney disease (CKD). There are several reasons why treatment of established cardiac risk factors is lacking, including weak evidence for efficacy or extrapolation of evidence from the non-CKD setting. Ongoing work is needed to better understand the epidemiology, pathophysiology, diagnosis, and treatment of CAD in kidney transplantation.

Fig:1:

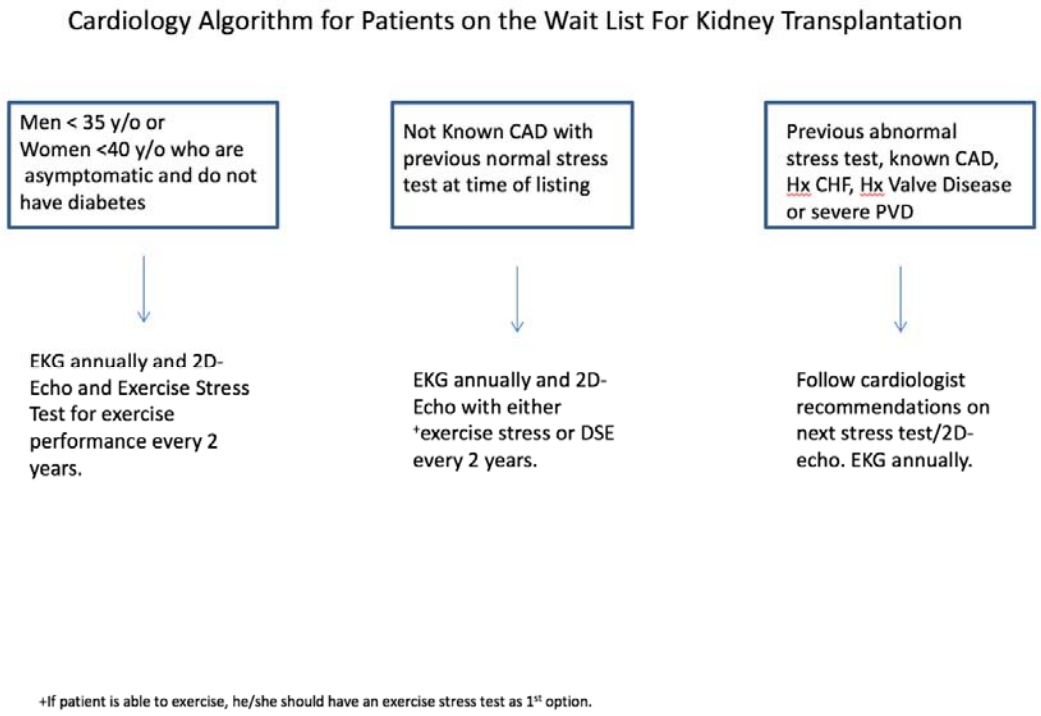
Cardiology Algorithm for Patients Being Worked Up For Kidney Transplantation



CAD: Coronary Artery Disease, CHF: Congestive Heart Failure, PVD: Peripheral Vessel Disease,

Fig: 2:

Cardiology Algorithm for Patients on the Wait List For Kidney Transplantation



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