Cardiovascular Disease in Live Related Renal Transplantation

A Kaul, RK Sharma**, A Gupta***, N Sinha†, U Singh‡

Abstract
Cardiovascular disease has become the leading cause of morbidity and mortality in renal transplant recipients, although its pathogenesis and treatment are poorly understood. Modifiable cardiovascular risk factors and graft dysfunction both play an important role in development of post transplant cardiovascular events. Prevalence of cardiovascular disease was studied in stable kidney transplant patients on cyclosporine based triple immunosuppression in relation to the various risk factors and post transplant cardiovascular events. Analysis of 562 post transplant patients with stable graft function for 6 months, the patients were evaluated for cardiovascular events in post transplant period. Pre and post transplant risk factors were analyzed using the COX proportional hazard model. 174 patients had undergone pre transplant coronary angiography, 15 of these patients underwent coronary revascularization (angioplasty in 12, CABG in 3). The prevalence of CAD was 7.2% in transplant recipients. Of 42 patients with CAD (73.8%) had cardiovascular event in post transplant period. Age ≥40 yrs, male sex, graft dysfunction, diabetes as primary renal disease, pre transplant cardiovascular event, chronic rejection showed significant correlation in univariate analysis and there was significant between age ≥40 years (OR=2.16 with 95%CI, 0.977 - 4.78) S creatinine ≥1.4mg %( OR=2.40 with 95% CI, 1.20 - 4.82), diabetes as primary disease (OR with 95% CI 3.67, 3.2-14.82), PTDm (OR 3.67, 95%CI 1.45-9.40), pre-transplant cardiovascular disease (OR 4.14, 95% CI 3.8-13.15) with post transplant cardiovascular event on multivariate analysis. There was poor patient and graft survival among those who suffered post transplant cardiovascular event. The incidence of cardiovascular disease continues to be high after renal transplantation and modifiable risk factors should be identified to prevent occurrence of events in post transplant period.

Introduction
Cardiovascular disease (CVD) is very common after renal transplant than in general population.1 Mortality and morbidity rates due to CVD in organ transplant accounts for more than 10 folds than in general population.2 As such these individuals die with functioning grafts, death resulting from CVD has become an increasingly important cause of graft loss, with 40% of deaths resulting from a Cardiovascular cause particularly after 1 year post transplant.3 There are no randomized controlled trials in transplant patients to prove that modifying risk factors reduces the incidence of CVD. The factors that lead to atherosclerosis in renal transplant population is similar to those described in general population including diabetes, hypertension, many of these are exacerbated by the immunosuppression administered to prevent allograft rejection.4 It is also possible that primary/secondary risk factors interventions are less effective in renal transplant recipient than in general population. Most studies suggest that there is a high prevalence of traditional risk factors for CVD and that these risk factors for CVD and that these risk factors correlated with CVD after transplant. Thus modifications of the traditional risk factors may help reduce the high incidence of CVD after renal transplant. Despite the importance of cardiovascular disease as a cause of death in other series, there is no data concerning the prevalence and risk factors in our country. The present study is to establish the prevalence of CVD in stable kidney transplanted patients and assess the risk factors that can have association with post transplant cardiovascular disease.

Methods
562 patients, 499 men and 63 women who under went live related renal transplantation between June 1989 to December 2002 with functioning graft for more than 6 months were randomly analyzed with the objective to examine the prevalence of cardiovascular disease in renal transplantation and to analyze the risk implicated in development of these events. This was also to look into the clinical markers useful to identify the high risk transplant patients. Ischemic heart disease was defined as historical evidence of anginal attacks/acute myocardial infarction on antianginal treatment, coronary revascularization/death due to ischemic event. Cerebrovascular disease was defined as thrombotic/embolic stroke or documented transient ischemic attack. Peripheral vascular disease was defined as amputation resulting from vascular insufficiency/ revascularization procedure. Hypertension was graded as 0 <130/85-90 while receiving no antihypertensive medication grade 1 = 130-140/85-90 with 1 or more antihypertensive medication, grade 2 > 140/90 with 1 or more medication. Following data were recorded: Age at transplantation, gender, underlying renal disease, mode of dialysis, history of systemic hypertension - pre and post transplant, history of cardiovascular event before transplantation, type of immunosuppression, erythrocytosis, blood sugar control, acute rejection episodes, development of PTDm, withdrawal of cyclosporine, and antihypertensive medications. Biochemical parameters analyzed were hematology, renal functions, lipid profiles, cyclosporine levels, proteinuia. Statistical analysis was performed with the student’s t-test for numerical variables and with the chi –squared
### Table 1: Comparison of potential cardiovascular risk factors in patients with or without cardiovascular disease.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group A n=42 (%)</th>
<th>Group B n=520 (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥40 yrs</td>
<td>31(73.8%)</td>
<td>195(37.5%)</td>
<td>0.000</td>
</tr>
<tr>
<td>Male gender</td>
<td>41 (97%)</td>
<td>458 (88.01%)</td>
<td>0.059</td>
</tr>
<tr>
<td>Diabetes at Tx</td>
<td>23 (54.7%)</td>
<td>63 (12.1%)</td>
<td>0.000</td>
</tr>
<tr>
<td>Post tx DM</td>
<td>6 (14.2%)</td>
<td>41 (7.8%)</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic hypertension ≥140 mmHg</td>
<td>35 (7.7%)</td>
<td>419 (92.3%)</td>
<td>NS</td>
</tr>
<tr>
<td>H/o HTN pre tx</td>
<td>40 (95.2%)</td>
<td>492 (94%)</td>
<td>NS</td>
</tr>
<tr>
<td>Pre Tx cardiovascular disease</td>
<td>11 (26.2%)</td>
<td>41 (7.8%)</td>
<td>0.000</td>
</tr>
<tr>
<td>More than 2 antihypertensive/</td>
<td>27 (64.2%)</td>
<td>303 (58.2%)</td>
<td>NS</td>
</tr>
<tr>
<td>day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum creatinine ≥1.4mg%</td>
<td>31 (73.8%)</td>
<td>277 (53.2%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Erythrocytosis (HCT &gt; 51%)</td>
<td>6 (14.2%)</td>
<td>67 (12.8%)</td>
<td>NS</td>
</tr>
<tr>
<td>On cyclosporine after one year</td>
<td>36(87.5%)</td>
<td>432 (83.07%)</td>
<td>NS</td>
</tr>
<tr>
<td>Post transplant HTN ≥140 mmHg</td>
<td>38 (90.47%)</td>
<td>447 (85.9%)</td>
<td>NS</td>
</tr>
<tr>
<td>Cholesterol ≥200 mg%</td>
<td>11 (26.2%)</td>
<td>138 (26.5%)</td>
<td>NS</td>
</tr>
<tr>
<td>Triglyceride ≥150mg%</td>
<td>10 (23.8%)</td>
<td>132 (23.28%)</td>
<td>NS</td>
</tr>
<tr>
<td>HDL ≤40 mg%</td>
<td>12 (28.5%)</td>
<td>142 (27.8%)</td>
<td>NS</td>
</tr>
<tr>
<td>Chronic rejection</td>
<td>16 (38.9%)</td>
<td>129 (24.8%)</td>
<td>0.058</td>
</tr>
</tbody>
</table>

(χ2) test for nominal data. Multiple logistic regression using COX-proportional hazard model was used to determine the risk factors related to cardiovascular disease. Statistical significance was defined as a P < 0.05.

### Results

Out of the 562 patients who underwent live related renal transplantation with mean age of 36.7±11.05 years had an average follow up 41.07±23.27 months. 88.8% of these patients were male, while the cause of end stage renal disease was diabetics in 15.3%, CGN in 54.3% and CIN in 25.1% patients. 522 patients received azathioprine + Cyclosporine + Prednisolone based immunosuppression while 40 patients were on MMF + cyclosporine + Prednisolone. 16.7% were electively withdrawn off cyclosporine at 1 year after transplantation. 8.9% recipients had elderly donors age > 65 yrs and 5.3% donors were hypertensive requiring 1 antihypertensive medication.

Detection of pre transplant cardiovascular disease in ESRD population was assessed by angiography done on all diabetics and patients aged ≥45yrs with or without clinical suspicion of CAD. Of the 174 angiographies done revealing mild to moderate in 33 and severe stenosis in 16 cases, 12 underwent angioplasty while 3 underwent CABG in the pre transplant period. 3 of these patients had suffered from cerebrovascular accident in the pre transplant period. Thus prevalence of cardiovascular disease occurred in 9.2 % in the pre transplant period.

42 patients (7.2%) developed cardiovascular event in the post transplant period i.e. 38 patients (6.7%) had ischemic heart disease, 3 of them had cerebrovascular event and another one with peripheral vascular disease 11 of them had manifested CVD prior to transplant. 3 patients who had pre and post transplant CAD died of sudden cardiac death. The patient outcome with those who had cardiovascular event on subsequent follow up reveal that 5 (11.9%) had cardiac event as a cause of death while14 (33.3%) had cause of death unrelated to cardiac etiology, 3 (7.1%) were back on dialysis in view of advanced renal failure. These 42 (7.4%) patients who suffered with cardiovascular event in post transplant period were older at the time of transplant (46.02±11.2 yrs vs 36.04±11.2 yrs, P value=.000) predominantly males (97.0% vs 88.01%, P value=.059), with basic disease as diabetics (54.76% vs 12.1%, P value=.000), graft dysfunction i.e S creatinine >1.4 mg% at follow up (73.80% vs 53.2%, P value=.01) with higher occurrence of chronic rejection in the event population (38.09% vs 24.8%, P value=.058). Pre transplant cardiovascular event had significant correlation with post transplant event (26.1% vs 7.88%, P value=.000) (Table 1). There were no differences in prevalence of acute rejection episodes and their treatment, use...
of cyclosporine dyslipidemia, or post transplant hypertension and erythrocytosis between the two groups.

Multivariate analysis using COX proportional hazard model showed that age at transplant i.e. ≥40 years (OR=2.16, 95% CI 9.77-4.78), Diabetes as primary renal disease (OR=6.9, 95% CI 3.2-14.82), graft function serum creatinine ≥1.4mg %) OR=2.40, 95% CI 1.20-4.82), PTDm (OR=3.67, 95% CI 1.45-9.40), pre transplant Cardiovascular event (OR=4.14, 95% CI 38-13.15) were the risk factors of Cardiovascular disease (Table 2). Kaplan Meier demonstrated a poor patients and graft survival among those who suffered with a cardiovascular event in the post transplant period (Figures 1, 2).

Discussion

Kasiskie et. al. observed in his study population the prevalence of ischemic heart disease (by medical history) was 9.5%, cerebrovascular disease was 3.7%, whereas the prevalence of all cardiovascular disease was 12.9% at the time of transplantation. Unfortunately, ischemic heart disease is often asymptomatic in patients with End stage renal disease and so a routine history and physical examination may not be adequate to detect potentially life threatening disease. Cardiovascular event in our study population was about 9.2% in the pre transplant period with prevalence in post transplant period to be 7.4%. The cause for such low prevalence could be due to use of intervention in those who were either symptomatic or diabetics and could be a major reason in missing a majority of patients with cardiovascular disease.

Mean age of patient and sex increases the relative risk of death from cardiovascular event, both being unmodifiable factors for CV morbidity. Both had statistical significance in our study population also; however the males transplanted were more in this study population and could be one of the reasons of its statistical significance besides female sex is protected from occurrence of Cardiovascular event in the pre menopausal period under the influence of sex hormones.

Arterial hypertension is a frequent complication post transplant accounting for 50-80% with negative effects on graft and patient survival. Multiple studies have demonstrated that patient who developed hypertension had a high cardiovascular risk for an event, this correlation however did not reach statistical significance in our study group. In our study, neither the pre nor the post transplant systemic hypertension was strongly associated with the occurrence of event which could be possibly due to the crude index used to measure the effects of hypertension and did not adequately reflect the degree and duration of Blood Pressure elevation after transplantation. It could be possible that aggressive treatment as appreciated by the use of antihypertensive in both groups which could be the reason of its not reaching statistical significance, effectively reducing the adverse events in our study population.

PTDM in the multivariate analysis stood as a risk factor to occurrence of cardiovascular event, so have the others seen with increased mortality after transplantation. It is unclear whether it occurrence directly influences the pathogenesis of the vascular event and could be due the relationship of glycemic control and the occurrences of micro and macro vascular complication of diabetes which is well established. The prevalence of PTDM ranges between 5-20% and was around 8.37% in our series. Diabetes is an important CVD risk factor in transplant population. Kasaki et al found diabetes was associated with 40% increase in incidence of IHD which was also appreciated in our study population.

Various studies have demonstrated that dyslipidemia is an important risk factor in this set of population while the other s had not observed significant correlation which may be due to differences in defining dyslipidemia. This however was also not significantly related to the event in our study. In explanation to this discrepancy could be that more number of patients who had the lipids profile available belonged to the control group. Goel et al had shown lower levels of total cholesterol and LDL with patients with CAD in Indian population. Early graft dysfunction has been classically used as a marker of graft survival and in our study this was associated with increased cardiovascular event, and was responsible for the poor graft survival. Studies have shown significant increased prevalence of obesity, impact of cyclosporine and steroids on systemic hypertension. Role of cyclosporine in the occurrence of event was not observed in our study population, this could be due to the fact that more patients were off cyclosporine in the control group. These could be possible reasoning for non-significant association between the event and role of immunosuppression. Thus present study shows significant correlation between age, diabetic as primary renal disease, PTDm, pre transplant cardiovascular event, graft dysfunction with post transplant event.

Recently ethnicity has been identified as a contributor to development of cardiovascular disease following renal transplantation. Post transplant major adverse cardiovascular event (MACE) rates, a composite of MI, coronary intervention, and cardiac death, were significantly greater in South Asians when compared with whites, blacks, and even East Asian individuals, report investigators. South Asians have a lot of diabetes and a lot of metabolic syndrome, so they do get cardiovascular disease at a rate much higher than is seen in the general population however when patients develop chronic kidney disease, that alone puts them at higher risk of heart disease. So when a South Asians get a kidney transplant or kidney disease they have two major risk factors: chronic kidney disease and their ethnicity. The study included 864 kidney recipients transplanted at St Michael’s Hospital in Toronto between 1998 and 2007 and followed until June 2009 including the analysis on 139 South Asian, 550 white, 65 black, and 110 East Asian individuals, all with similar baseline risk, including preexisting cardiac disease. South Asian ethnicity was classified as individuals from India, Pakistan, Bangladesh, Sri Lanka, Nepal, Maldives, or Bhutan. The MACE rate among South Asians was 4.4 per 100 patient-years of follow-up compared with 1.31 per 100 patient-years of follow-up in whites. The MACE rate among transplant patients of black and East Asian descent was 1.16 and 1.61 per 100 patient-years follow-up, respectively. The MACE rates beyond three months were 25.1% for South Asians, 10.2% for whites, 10.7% for blacks, and 9.0% for East Asians. Similarly, the rates of MI were 21.5% for South Asians, 8.7% for whites, 7.6% for blacks, and 7.2% for East Asians.

In a multivariate Cox regression model, age and South Asian descent were significant risk factors for the development of major cardiac events beyond three months after transplant, with South Asian ethnicity increasing the risk nearly 3.5 times compared with individuals of European descent. The analysis looking at events beyond three months was designed to limit the impact of baseline comorbidities—individuals with events in the first three months likely have more underlying disease—as well as the effects of the stress of surgery and hospitalization. South Asian kidney-transplant patients also had more events in the first three months.
Conclusion

Despite newer immunosuppressive protocols and more effective management of risk factors, cardiovascular disease continues to be a major cause of morbidity and mortality after renal transplant. The treatment of risk factors known to be modifiable must be effective and must be introduced early in the course of renal failure, well before the need for Renal Replacement Therapy and may be continued after transplant. Hopefully this will translate into a reduction of cardiovascular mortality and better long term survival of these patients.

References


Nomination for the Post of Vice President

Nominations are invited to fill the vacancy for the post of “Vice President” of The Association of Physicians of India.

Eligibility: The candidate should be a life member of API for at least 5 years and should have completed at least one continuous full term of 3 years in any elected position in the Governing Body.

The application should be duly proposed and seconded by two valid members of API and reach the Hon. General Secretary of API, Dr. Milind Y. Nadkar, Unit No. 6 & 7, Turf Estate, Opp. Shakti Mill Compound, Off. Dr. E. Moses Road, Near Mahalaxmi Station West, Mumbai – 400 011 not later than 30th November 2011. Applications that are received after the due date will not be considered. The last date for withdrawal of nomination is 20th December 2011. The valid nominations shall be placed before the Governing Body for electing the incumbent.

The nomination paper for elections should be downloaded from the website of API www.apiindia.org

Doctor 2010 - Medical Software

Compatible with Windows 7, Vista, XP, Desktop, Laptop and Netbook

Clinical: Case sheets, specialties sheets, Inpatient, ICU, Lab, PDR, Auto Casesummary, Certificates, letters, USS, X-ray, Pathology, Endoscopy, Echo, Proc. reports, very little typing needed. Prescription Autodose, Allergy, disease-contraindication, interaction alert, Fonts option (Hindi Tamil etc) Overdose treatment, Ther. level, dose in organ failues Store Recall at a single click. Sends auto SMS & Email reminder, bills due, reports, mass SMS, appointments thro web. and patient OP Queue List LCD dynamic display option extra.


Store/Link photos, X-ray, ECG, Videos; Change Header/Footer; Diet advisor-autocalory calculator

Educative: Disease guidelines Medical graphs; Patient education videos & prinouts. Reliable. Saves Life, Time

Money. Hospital pack, and excl. medicine, surgery, OBG, clinic packs available. Rs.9500 only E-mail: medisoftindia@gmail.com

Address: MEDISOFT, Achutha Warrier Lane, Cochin-682035 www.medisoftindia.com Ph: 09847294414