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Review Article

Cardiovascular disease: Prevention and treatment in renal transplant recipients

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ARTICLE INFO

Article history:
Received 18 October 2013
Accepted 25 November 2013
Available online 11 December 2013

Keywords:
Cardiovascular disease
Renal replacement therapy
Allograft rejection

ABSTRACT

Despite improved survival, renal transplant recipients remain at a high risk of increased mortality and mortality from cardiovascular disease. Both traditional cardiovascular disease (CVD) risk factors and those unique to this population add to the burden of disease, making their CVD risk 50 times that of the general population. This article discusses our present understanding of cardiovascular disease, the risk factors, including dyslipidemia, hypertension, allograft rejection and dysfunction, anemia, proteinuria and new onset diabetes after transplantation (NODAT), as well as prevention and management of these risk factors. Cardiovascular interventions as well as future considerations are also briefly discussed.

1. Introduction

For patients with end stage renal disease (ESRD), renal transplantation is considered to be the best form of renal replacement therapy (RRT). When compared to patients on dialysis, transplantation is expected to provide a better quality of life as well as improved survival by about 10–20 years.[1,2] However, the long-term survival of renal transplant recipients does not approach that of their otherwise healthy compatriots, owing mainly to increased cardiovascular morbidity and mortality[3] with about half dying with a functioning allograft,[4] and cardiovascular disease (CVD) and cerebrovascular accidents (CVA) accounting for half these deaths.[5,6] The annual CVD related risk is about 3.5–5%.[7–9] The risk of developing premature CVD in an ESRD patient is ten to 20 times that of the general population and a successful transplantation substantially reduces the risk to three to five times and is more pronounced in younger patients.[10–12] (Also see Fig. 1).

The mortality risk in the renal transplant recipient continues throughout the post-transplant period and persists up to allograft failure. Data from the United States Renal Data System (USRDS) estimates that about 40% of recipients experience a cardiovascular event in the first three years post renal transplant.[13] The burden of CVD in renal transplant recipients is a combination of multiple traditional and non-traditional risk factors, the latter includes pre-transplant disease and undesired results of immunosuppressive therapy. This article attempts to highlight the importance of some of these risk factors as well as prevention and management of CVD in these patients.

2. Etiology of CVD in renal transplant recipients

It is unfortunate that CVD is often presumed to imply coronary artery disease (CAD) unlike the general population where the two may be more synonymous. Although myocardial infarction is common in renal transplant recipients, two other common presentations are those of congestive heart failure

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2211-9477/$ – see front matter
http://dx.doi.org/10.1016/j.cqn.2013.11.007

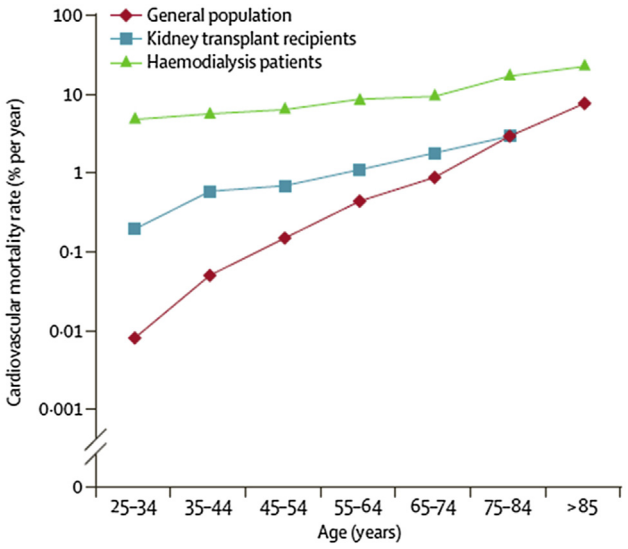

Fig. 1 – Mortality from CVD in transplant recipients, ESRD patients and general population.[11,12]

(CHF) and sudden cardiac death, presumably due to arrhythmias.[14–16] CHF is the second most common cause of hospitalization in renal transplant recipients[17] more so in the elderly and the diabetics.[14] Though CAD is indeed common, CVD is quite often the result of altered ventricular function and geometry. This condition has been termed "cardiomyopathy of overload"[18] or uremic cardiomyopathy, a term describing the structural and functional cardiac abnormalities resulting from the pre-transplant uremic milleu[19] (Fig. 2).

3. Traditional risk factors

The Third Report of the Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III, or ATP III) from the National Cholesterol Education Program (NCEP)[20] described major risk factors for the development of CAD. These are listed below (see Table 1) and are probably as important in transplant recipients as in the general population. The importance of other traditional risk factors predisposing to CVD like obesity, (especially abdominal obesity), family history of premature CAD, sedentary lifestyle, ethnicity and psychosocial factors have not been rigorously studied in transplant recipients but are probably important.[22] CVD risk is probably a continuum and increases akin to dose response, i.e. more the number of risk factors, duration of exposure and severity of risk, higher the CVD risk. While true of the general population, this awaits confirmation in renal transplant recipients.

4. Additional risk factors of CVD in renal transplant recipients

Renal transplant recipients have additional risk factors not shared with the general population as a result of the underlying or past kidney disease and specifically related to kidney transplantation. The contributions of some of these non-traditional risk factors are discussed below.

4.1. *Post-transplant dyslipidemia*

An elevated level of plasma lipids is a frequently encountered post-transplant complication. About 40% of recipients develop hypercholesterolemia while about 6% have hypertriglyceridemia.[23] These changes begin early in transplantation with elevation in total cholesterol, LDL cholesterol, by 1–1.5 mmol/L (about 38–58 mg/dL) and smaller increase in HDL cholesterol and triglyceridemia by sixth post-transplant week.[24] The concentration of intermediate lipoprotein that are specially atherogenic also increase.[25] Dyslipidemia contributions to CAD and CVD risk and has also have association with reduced graft survival.[26] Immunosuppressive medications decrease the risk of allograft rejection but this comes with the price of increased CVD risk.[5]

Long-term corticosteroids, even at low doses, cause dyslipidemia.[27] Calcineurin inhibitors, especially cyclosporine contribute to post-transplant dyslipidemia[28] as do proliferation signal inhibitors or mammalian target-of-rapamycin inhibitors (PSI/mTOR) in a dose-dependent manner.[29,30] It may be possible that despite the elevated plasma lipids associated with mTOR inhibitors, the CVD risk may not be elevated because of their antiproliferative effect on vascular endothelium.[31] Mycophenolate mofetil and azathioprine have not been implicated in the etiology of post-transplant dyslipidemia.

4.2. *Hypertension*

Presence of systolic blood pressure (SBP) > 140 mmHg or diastolic blood pressure (DBP) > 90 mmHg qualifies the diagnosis of hypertension in the renal transplant recipient as per the Seventh Report of the Joint National Committee on Prevention, Detection, and Evaluation of High Blood Pressure (JNC VII).[32] The prevalence of hypertension is between 75 and 90% of renal transplant recipients,[5,33,34] a figure that has not changed remarkably with time.[35,36] In the large Collaborative Transplant Study, about 55% of the total cohort of 29,751 patients had blood pressures that were uncontrolled.[37] The hypertensive renal transplant recipients were observed to have poor long-term allograft survival.[38] In another retrospective cohort of 1666 renal transplant recipients, elevation of SBP of only 1 mmHg was associated with an 18% increase in death and 17% increase in death-censored graft failure.[39] Similar observations were made in two other reports.[8,35]

The etiology of hypertension in renal allograft recipients is multi-factorial.[40,41] The possible contributors include obesity,[42] presence of delayed graft function, rejection episodes, corticosteroids, preexisting hypertension, calcineurin inhibitors (CNI), presence of delayed graft function (DGF), quality of donor kidney, renal artery stenosis in the transplanted kidney,[43] chronic graft dysfunction and native kidney disease i.e. etiology of CKD pre-transplant. Of these, the most important contributors possibly are CNI based immunosuppression and preexisting hypertension,[36] the latter being present in nearly half the renal transplant recipients.[7] CNIs,