Cardiovascular Disease After Kidney Transplant

Nitesh N. Rao, MBBS, MD, FRACP,[*] and P. Toby Coates, MBBS, FRACP, PhD[*,†]

Summary: Renal transplantation is the preferred treatment for patients with end-stage kidney disease. However, despite successful kidney transplantation, cardiovascular disease (CVD) remains one of the major causes of patient death and hence graft loss. The antecedents of this increased risk reside within the development of end-stage kidney disease and dialysis. Risk factors for the development of CVD include diabetes, hypertension, and dyslipidemia. Other transplant-specific factors include the presence of a patent arteriovenous fistula and immunosuppressive therapy. Efforts to modify these factors should be strongly encouraged to improve long-term outcomes of transplant patients and reduce death from CVD in this at-risk patient population.
Semin Nephrol 38:291-297 © 2018 Published by Elsevier Inc.
Keywords: Cardiovascular disease, kidney transplantation

Cardiovascular disease (CVD) after kidney transplantation remains one of the leading causes of death for patients with end-stage kidney disease (ESKD).[1] With increasing numbers of patients requiring a transplant, better identification of cardiac risk is required to prevent premature death with a functioning graft. Because there is increasing pressure resulting from greater dialysis numbers to increase acceptance rates into transplant programs, it is likely that more patients with a higher cardiovascular disease burden entering dialysis will be candidates for transplantation.[2] Thus, the challenge is to increase access to transplantation and improve long-term outcomes, reducing the loss of kidneys owing to premature death from cardiovascular disease is therefore a pressing clinical need.[3]

CV risk remains high even after kidney transplantation (KTx) (including in patients with normal serum creatinine concentration).[4] Table 1 summarizes common cardiac manifestations in renal transplant recipients. There is a two- to three-fold higher incidence of congestive heart failure despite KTx and a two-fold higher risk of death.[5] A CV cause accounts for 17% to 40% of deaths occurring in kidney transplant recipients.[6] The prevalence of coronary artery disease in kidney transplant recipients is estimated to be approximately 15%, whereas that of left ventricular hypertrophy is 50% to 70%.[7,8] Overall, the incidence of CV disease is at least three to five times that of the general population.[9] In a recent prospective study from Canada the incidence of major adverse cardiac events after kidney transplant was quantified at 7% over a 4-year period.[10] Hence, the prevalence of cardiovascular disease in kidney transplant recipients is therefore high, making this an important challenge for physicians involved in transplant patients' care.[11]

Various factors contribute to cardiovascular structural abnormalities in patients with CKD and those on dialysis, which creates the background for CVD after undergoing transplant. These include factors that increase volume overload such as sodium and water retention, chronic anemia, and also functioning arteriovenous fistulae. Pressure overload occurs mainly owing to hypertension, arteriosclerosis, and aortic stenosis, if present. After a successful kidney transplant, many of these factors including sodium and water retention, chronic anemia, hypertension, and arteriosclerosis improve.[12–14]

PRETRANSPLANT RISK FACTORS FOR POST-TRANSPLANT CARDIOVASCULAR DISEASE

The antecedents for CVD after transplant arise in the pretransplant period during the development of ESKD and include hypertension, dyslipidemia, diabetes, and lifestyle factors. In the general population the risk factors for coronary artery disease are well recognized as being hypertension, hyperlipidemia, smoking, and diabetes (Table 2).[15] Although patients on dialysis have a higher risk of CVD (estimated to be 10-20 times greater), renal transplantation lowers the risk, but not back to the level of the general population.[16] Conventional risk factors such as diabetes, hypertension, and dyslipidemia contribute to the risk of CVD

[*]*Renal Unit, Lyell McEwin Hospital, Elizabeth Vale, South Australia.*
[†]*Central Northern Adelaide Renal and Transplantation Service, Royal Adelaide Hospital, Adelaide, South Australia.*

Financial support: none.

Conflict of interest statement: Kunihiro Matsushita has received research funding and personal compensation as a consultant from Kyowa Hakko Kirin and an honorarium from Daiichi Sankyo.

Address reprint requests to P. Toby Coates, MBBS, FRACP, PhD, Kidney and Islet Cell Transplantation, Royal Adelaide Hospital, Port Road, Adelaide, South Australia, Australia. E-mail: Toby.Coates@sa.gov.au

0270-9295/ - see front matter

https://doi.org/10.1016/j.semnephrol.2018.02.008

Table 1. Common Cardiac Manifestations in Renal Transplant Recipients

Coronary artery disease/myocardial infarction
Sudden cardiac death, likely from arrhythmia
Congestive heart failure
Valvular heart disease, such as aortic sclerosis
Atrial fibrillation
Pulmonary hypertension

after transplant, but other factors specific to transplant also play a role. Systemic inflammation, infection, and immunosuppressive medication play a role in CVD risk (Table 3).[17,18]

Diabetes mellitus is a major risk factor for the development of post-transplant CVD. Both glucose intolerance and post-transplant diabetes are important risk factors for the development of post-transplant CVD.[19] In the Symphony Study, which compared cyclosporine (low and standard dose), sirolimus, and low-dose tacrolimus, the rate of diabetes was 4.8% to 10.6% for all of the treatment arms.[20] Two recent studies also addressed this important issue. In a single-center study from the Mayo clinic, Keddis et al[21] found a significant improvement in outcomes for patients with type 2 diabetes mellitus, which they attributed to greater use of cardiovascular medications during the period from 1996 to 2012. However, in another registry-based publication, Lim et al[22] studied 980 patients from the Australian and New Zealand Dialysis and Transplantation Registry (ANZDATA) registry

Table 2. Pretransplant Risk Factors Leading to Cardiovascular Disease in Kidney Transplant Recipients

Traditional risk factors
Hypertension
Diabetes mellitus
Dyslipidemia
Left ventricular hypertrophy
Pre-existing heart failure
Coronary artery disease
Smoking
Increased body mass index
Sedentary lifestyle
Age
Nontraditional risk factors
Hyperhomocysteinemia
Anemia
Arteriovenous fistula
Systemic inflammation
Infections
Proteinuria
Dialysis vintage
Hyperfibrinogenemia
Homoarginine deficiency

Table 3. Post-Transplant Risk Factors Leading to Cardiovascular Disease in Kidney Transplant Recipients

Drug-induced hypertension
Drug-induced metabolic syndrome
Post-transplant diabetes
Functioning arteriovenous fistula
Recurrent infections
Altered estimated glomerular filtration rate
Deregulated calcium phosphate metabolism
High FGF-23 level

from 1994 to 2012 and found no evidence of improvement in survival after transplant for patients with type 2 diabetes mellitus over this period. The adjusted risk hazard ratio (HR) for death from cardiovascular disease in this study did not change (2.55; 95% confidence interval [CI], 1.94-3.36). Importantly, the adjusted risk of cardiovascular death was highest in younger recipients (age, <40 y) with a hazard ratio of 7.1, with patients between 40 and 55 years next with a HR of 2.5, and patients older than age 55 years with a hazard ratio of 1.54 for CV death. Interestingly, patients older than 65 years, as a prespecified group in this analysis, did not show an increased risk of CV death.

Hypertension remains an important cause of CV events in the KTx population and it has been observed that between 55.5% and 93% kidney transplant recipients have a systolic blood pressure (SBP) greater than 140 mm Hg. Opelz et al[23] investigated the effect of a decrease in BP among renal transplant recipients in the Collaborative Transplant Study database on long-term graft and patient survival. Patients whose SBP was greater than 140 mm Hg at 1 year after transplantation but controlled to 140 mm Hg or less by 3 years had significantly improved long-term graft outcome compared with patients with a sustained high SBP at 3 years (relative risk, 0.79; CI, 0.73-0.86; $P < .001$). In patients with ESKD who are potential recipients of a kidney transplant, up to 30% have evidence of congestive cardiac failure and approximately 75% have evidence of left ventricular hypertrophy.[15,24] A major factor that influences cardiovascular morbidity is pressure overload related to hypertension and atherosclerosis coupled with circulatory volume overload, which are well established to be present in the kidney failure population. It is well established that cardiac left ventricular mass predicts cardiovascular events both in ESKD patients and in patients after renal transplant.[25]

Dyslipidemia

In the general population, dyslipidemia is an important cardiovascular risk factor. In the transplant patient, Ong et al[26] observed that hypercholesterolemia was