Graft dysfunction and cardiovascular risk—an unholy alliance

Francese Moreso and Josep M. Grinyo

Department of Nephrology, Hospital Universitari Bellvitge, Department of Medicine, Universitat de Barcelona, Spain

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Introduction

Patients with progressive chronic renal failure on dialysis treatment and renal transplantation have an elevated mortality in comparison to the general population [1,2]. Despite the fact that renal transplant recipients are highly susceptible to infection and malignant disease, these patients mainly die of premature cardiovascular disease (CVD). Despite the fact that classical cardiovascular risk factors are highly prevalent in renal transplants, the Framingham heart score that considers patient’s age, dislipidaemia, hypertension, diabetes and cigarette smoking as risk factors underestimates cardiovascular risk in these patients, suggesting that other factors may also play an important role [3]. These non-traditional cardiovascular risk factors include increased oxidative stress, elevated biomarkers of inflammation, anaemia, calcium-phosphate metabolism imbalance, hyperhomocystinaemia or left ventricular hypertrophy [4]. Furthermore, a link between degree of renal function and CVD in the general population and renal transplants has been demonstrated [5,6].

Cardiovascular risk in renal transplants

Patients with end-stage renal failure have a 10–20-fold increase in cardiovascular mortality compared to the general population, but patients who receive a kidney transplant have a better long-term survival than patients who remain on the kidney waiting list [1]. In a large longitudinal study of mortality in patients who were receiving long-term dialysis, the standardized mortality ratio for all patients on dialysis, patients on dialysis who were awaiting transplantation and patients who received a kidney transplant were 16.1, 6.3 and 3.8 per 100 patient-years, respectively [1].

CVD is a general definition that includes coronary artery disease, congestive heart failure, valvular cardiac disease, stroke and peripheral vascular disease. The contribution of these different categories of CVD on cardiovascular mortality has often not been reported in large epidemiological studies.

The high incidence of coronary heart disease after renal transplantation is partly explained by the...
high prevalence of classical cardiovascular risk factors among renal transplants, the risk associated with diabetes mellitus being of special relevance [3]. This result has been confirmed in a prospective study that also showed C-reactive protein and hyperhomocystinaemia as independent risk factors for coronary heart disease [7]. Moreover, in a cohort of 922 patients from a single centre, ischaemic heart disease was mainly related with classical risk factors but the presence of multiple acute rejection episodes, overweight and time on dialysis before transplant were also identified as transplant-related risk factors [8]. It should be noticed that in this study, both fatal and non-fatal cardiovascular events were recorded, the latter representing more than 70% of total episodes. In contrast, one large epidemiological study showed that the rate for acute myocardial infarction among transplants may be close to the non-chronic kidney disease cohort [2]. Nevertheless, it is important to note that the risk reduction for acute myocardial infarction with transplantation vs waiting list varies by patient population and time after transplantation [9]. Furthermore, it has been proposed that the role of classical cardiovascular risk factors is especially relevant in renal transplants with the lowest cardiovascular risk [7].

In a multicentre study performed in Canada, it has been shown that the incidence of de novo congestive heart failure after renal transplantation is similar to the incidence of de novo ischaemic heart disease and implies a similar deleterious prognosis. The incidence of congestive heart failure was two to five times higher than the incidence in the general population, while the incidence of ischaemic heart disease was similar to that observed in the general population [10]. Thus, the authors propose that renal transplantation seems to be associated more with a state of ‘accelerated heart failure’ than to ‘accelerated atherosclerosis’. In this study, blood pressure and anaemia were identified as modifiable independent risk factors for congestive heart failure.

Valvular calcification is highly prevalent in end-stage renal disease patients and has been related to elevated calcium–phosphorus product. It has been shown that progressive renal failure is also associated with mitral annular calcification, which is a powerful predictor of atrial fibrillation, stroke and cardiovascular mortality [11]. Up to now, information on the evolution of valvular disease or appearance of de novo valvular disease after renal transplantation is scarce.

The incidence of stroke after renal transplantation ranges between 5% and 8%, at 5 and 10 years, respectively [12,13]. It has been proposed that the prevalence of haemorrhagic origin is higher than in the general population, involving between 15% and 40% of episodes. This event is related to aging, diabetes, hypertension and atherosclerosis. Recently, it has been also related to peritoneal dialysis as the modality of renal replacement therapy before transplant and with graft dysfunction [8].

Graft dysfunction as a cardiovascular risk factor

In renal transplants, the implantation of a single kidney combined to different injuries after transplantation leads to chronic graft dysfunction. Epidemiological studies have shown that about 60% of renal transplants have a glomerular filtration rate <60 ml/min/1.73 m² and about 15% <30 ml/min/1.73 m² at 1 year [14,15].

The analysis of about 60 000 adult patients registered in the United States Renal Data System receiving a primary renal transplantation between 1988 and 1998 has allowed to establish a strong association between serum creatinine at 1 year and cardiovascular death. As expected, this association was even closer when cardiovascular death after graft loss was included in the analysis. Moreover, this relationship follows a dose-dependent pattern, supporting the fact that decreased renal function is linked to CVD and is not only a simple coexistent condition [6].

The Assessment of Lescol in Renal Transplantation (ALERT) trial was a randomized, double-blind and parallel group study, aimed at exploring the effects of fluvastatin on cardiac and renal endpoints in renal transplants. In the placebo group, involving more than 1000 patients, baseline serum creatinine was associated with all-cause (relative risk per 100 µmol/l [RR]: 2.5), non-cardiovascular (RR: 2.3) and cardiac mortality (RR: 2.94) [16,17]. In the placebo group, baseline serum creatinine was not associated with non-fatal myocardial infarction or stroke [17]. Conversely, in a single centre study a serum creatinine >141 µmol/l was associated with a 3-fold risk for cerebrovascular events, but not for cardiac events [8]. Taken together, these results suggest that graft dysfunction is an additional risk factor for CVD in renal transplants but its impact on the different categories of cardiovascular events will require further studies to be well characterized.

On the other hand, chronic graft dysfunction is usually associated with proteinuria and the degree of proteinuria has been also associated with CVD. In renal transplants, about 15% of patients showed a urinary protein excretion >0.5 g/day at 1 year and even this low-grade proteinuria is an independent predictor from renal function of cardiovascular mortality [18,19]. Moreover, a retrospective study has suggested that renin–angiotensin system blockade may improve patient survival after renal transplantation [20].

Mechanisms linking graft function and cardiovascular risk

Mechanisms linking renal allograft dysfunction and CVD have not been clearly elucidated. This relationship is independent of classical Framingham risk factors and may be related with uraemia-associated factors, left ventricular hypertrophy, increased levels of inflammatory markers, hyperhomocystinaemia,
endothelial dysfunction, arterial stiffness or others. The relative contribution of these different factors to CVD has not been well characterized and the implication of their management on CVD in kidney transplant recipients has not been appropriately explored.

Uraemia-associated factors appear in patients with GFR <60 ml/min/1.73 m² and become especially relevant in those with GFR <45 ml/min/1.73 m². Important uraemia-associated factors are the decrease in the production of erythropoietin and active vitamin D and alterations in calcium/phosphorus metabolism. In a large multicentre study, it has been shown that anaemia is present in about 35% of renal transplants and the most powerful predictor among risk factors for post-transplantation anaemia was a serum creatinine >2 mg/dl [21]. Despite the fact that in patients with chronic kidney disease, correction of anaemia with epoetin improves left ventricular function and structure, this observation remains to be proven in renal transplants. Furthermore, left ventricular hypertrophy may be also related with extracellular volume expansion secondary to positive sodium balance, induced by renal dysfunction and enhanced by anticalcineurin agents. On the other hand, the prevalence of persistent hyperparathyroidism involves about 17–36% of patients during the initial years after transplantation and a significant deficit of calcitriol has been implicated in the pathogenesis of this persistent hyperparathyroidism [22,23]. The relationship between hyperparathyroidism and deficit of vitamin D and CVD in non-renal transplants patients has been extensively reviewed elsewhere [24] and very little data are available in renal transplants.

The link between inflammation and cardiovascular risk has been well established at different stages of chronic renal failure [4]. After transplantation, in the absence of rejection, inflammatory markers such as C-reactive protein, interleukin-6 or tumour necrosis factor-α initially decrease, approaching normal values and supporting the fact that restoration of renal function improves the inflammatory state induced by uraemia and/or dialysis [25]. However, an increase of interleukin-6 and tumor necrosis factor-α from 6 months after transplantation has been reported, suggesting that a persistent low-grade inflammation may also contribute to CVD in renal transplants [26]. Since this was a retrospective study involving a relatively small sample size, new well-designed and powered studies will further evaluate these results.

Persistent low-grade inflammation has been related with chronic infections such as periodontal disease and Chlamydia pneumoniae infection. In a cross-sectional study conducted in renal transplants, periodontal chronic disease and its concomitant systemic inflammatory reaction have been related with left ventricular hypertrophy [27]. On the other hand, chronic Chlamydia pneumoniae infection in renal transplants has been also related to cardiovascular death [28].

Plasma homocysteine concentration increases as graft function worsens and it has been shown that the relative risk for cardiovascular events increases 6% per μmol/l increase in total homocysteine, this association being independent from renal function [29]. In renal transplants, no attempts to analyse the possible interaction between homocysteine levels and renal function on CVD have been made. Randomized, placebo-controlled studies will determine whether homocysteine lowering decreases cardiovascular complications in renal transplants and whether this effect varies at different levels of graft function.

The role of endothelial dysfunction in chronic renal failure and its mediators such as endogenous inhibitor of NO synthase has been reviewed elsewhere [4]. The Hoorn study pointed out that endothelial dysfunction, but not markers of inflammatory activity, contributes to renal function-associated cardiovascular mortality in a population with mild renal insufficiency [30]. After transplantation, the improvement of endothelial function assessed by flow-mediated dilation of the brachial artery has been attributed to the elimination of uraemic toxins [31], but no studies have evaluated the relationship between endothelial dysfunction, graft dysfunction and CVD.

Finally, arterial stiffness is also a strong predictor of CVD and the compliance of small and large arteries decreases in the course of chronic kidney failure. After transplantation, oscillatory and capacitive artery compliance improves during the first month post-transplantation but returns to pre-transplantation values at 3 months [32]. It has been speculated that there is a possible vaso-active effect of calcineurin inhibitors that counteracts the benefit associated with improved renal function, this effect being more pronounced in tacrolimus than in cyclosporine-treated patients [33].

The above-mentioned studies suggest that the improved control of non-traditional cardiovascular risk factors, associated with the restoration of renal function after renal transplantation, partly explains the better outcome of patients receiving a kidney transplant than that of patients remaining on the kidney waiting list.

Conclusion

Graft dysfunction and proteinuria are linked to CVD in renal transplant patients. This relationship has been related with uraemia-associated factors, left ventricular hypertrophy, chronic inflammation, hyperhomocysteaemia, endothelial dysfunction or arterial stiffness, but the contribution of these factors to CVD has not been characterized. Since different strategies to improve renal function or reduce proteinuria may modify cardiovascular risk, prospective trials that consider different categories of CVD as primary endpoints are necessary. On the other hand, classical cardiovascular risk factors such as cigarette smoking, hypertension, glucose metabolism or dislipidaemia should be adequately managed in all patients.
Conflict of interest statement. Data in the present work have not been published previously in whole or part.

References


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