Cardiovascular disease after renal transplantation

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Cardiovascular disease after renal transplantation. Cardiovascular disease is a major hazard limiting the life expectancy of renal transplant recipients and the most frequent cause of late allograft loss. Patients with renal disease have usually been exposed for both traditional, and for them unique, risk factors over a prolonged period of time and may carry the burden of advanced atherosclerotic disease already at the time of transplantation. The observed survival benefit of transplantation is probably from elimination of the numerous uremia-related risk factors. However, immunosuppressive therapy and the chronic inflammatory state, together with genetic susceptibility and not infrequently impaired renal function, may bring about new potentially atherogenic conditions. Metabolic risk factors may jeopardize both patient and graft survival. Several observational studies provide evidence for the negative impact of pre-existing metabolic abnormalities on long-term outcomes. Identification of modifiable cardiovascular risk factors may enable risk reduction also in renal transplant recipients. Results of ongoing intervention trials are awaited. The observed improvement of patient survival after renal transplantation during the past decade may reflect the increasing awareness and more optimal care of patients throughout the course of renal disease.

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality both in patients with chronic renal disease and after successful renal transplantation. The burden of CVD exceeds by far that of the general population. Many of the traditional CVD risk factors are operative in renal transplant recipients (RTRs). In addition, several features unique to RTRs deserve specific attention.

EPIDEMIOLOGY OF CVD FOLLOWING RENAL TRANSPLANTATION

In spite of the substantial survival benefit of renal transplantation over long-term dialysis [1], transplant recipients have about four times higher mortality after the first year compared with the general population [2]. CVD events represent the single most frequent cause of death in RTRs accounting for 35–50% of all-cause mortality, and they occur at least twice as often as in the background population [2–6].

In the cyclosporine era, with improving success of transplantation, death with graft function emerged as the leading cause of graft loss after the first year, and it accounts for the majority of graft losses [3, 5]. Of deaths with a functioning graft, more than half are from ischemic heart disease (IHD) and other vascular diseases [3]. The risk of death from IHD was found to be 6.4 times higher in non-diabetic and 20.8 times higher in diabetic RTRs aged 55–64 years compared with the general population [3]. The risk for angina pectoris was increased 12–16 times in RTRs aged 40–49 years and 3–4 times in those aged 60–69 years [7]. Thus, CVD is a major threat to RTRs.

RISK FACTORS FOR CVD IN RTRS

The established risk factors for atherosclerotic vascular disease in the general population are present in RTRs and are probably also involved in the progression of renal disease [8]. The underlying renal disease resulting in ESRD is frequently a consequence of a disorder leading to atherosclerotic vascular disease per se, when renal disease is part or a consequence of this condition (e.g., diabetes, hypertensive nephrosclerosis). In addition, patients with renal disease have several other abnormalities that are consequences of renal disease and impaired renal function and which, in turn, may contribute to the development and progression of CVD. Furthermore, pharmacotherapy after transplantation may exert potential adverse effects on CVD manifestations. So, the preexisting and, to a various extent, persisting or recurring renal failure, proteinuria, ongoing inflammation, infections, immunosuppressive, and other therapy will modify the effect of traditional risk factors for CVD. Indeed, recent studies emphasize that the high incidence of IHD is underestimated by the risk factors identified in the general population [9].

Traditional risk factors

Predictors for CVD in the general population include non-modifiable factors such as age, gender, genetic background, and also numerous risk factors, which are more
or less modifiable by lifestyle changes and pharmacotherapy. Among the modifiable risk factors, obesity, smoking, hypertension, diabetes, hyperlipidemia, and hyperhomocysteinemia are best delineated. With better understanding of the pathogenic role of these risk factors and evolution of potent therapeutic agents with moderate side effects, effective modification of cardiovascular risk factors and reduction of CVD morbidity and mortality can be achieved in the general population [10]. This article will focus on some modifiable risk factors for CVD in renal transplant recipients.

**LIPID AND LIPOPROTEIN ABNORMALITIES IN RTRS**

Renal disease is associated with profound abnormalities in lipid and lipoprotein metabolism [11]. In RTRs, hyperlipidemia is a well-known feature. Factors with influence on post-transplant hyperlipidemia include age, body weight, pretransplant lipid levels, and, not unexpectedly, presence of proteinuria and allograft dysfunction. Immunosuppressive agents, in particular corticosteroids and cyclosporine, are important contributory factors [12]. Elevated total and LDL cholesterol occur in about 60% and hypertriglyceridemia in about 35%, whereas low HDL cholesterol is only present in 15% of RTRs [11]. In prospective studies, the time-dependent changes in cyclosporine- and prednisolone-treated patients are characterized by an increase in total, LDL, and HDL cholesterol while triglycerides remain unchanged [13, 14]. The lipoprotein profile may still become more atherogenic with triglyceride-rich small, dense LDL susceptible for oxidation [12]. Enhanced LDL oxidation is indicated by several studies and, of additional concern, both cyclosporine and tacrolimus have been implicated to increase LDL oxidation [15]. Tacrolimus, however, appears to have less negative impact on the lipid pattern [16]. Sirolimus, on the other hand, is well known for its propensity to cause hyperlipidemia, in particular hypertriglyceridemia [17].

Lipoprotein(a), Lp(a), is a risk factor for atherosclerotic vascular disease in the general population. Its specific apoprotein, apo(a), shows structural homology with plasminogen and Lp(a) can inhibit fibrinolysis. The size of apo(a) is genetically determined, and elevation of Lp(a) plasma levels shows an inverse relationship with apo(a) isoform size. Lp(a) is often elevated in patients with renal disease [18]. Cross-sectional studies in RTRs yielded conflicting results, but prospective studies demonstrate a decrease in Lp(a) levels following transplantation [15, 19]. The decrease in Lp(a) depends on apo(a) phenotype, and pretransplant Lp(a) levels, and is influenced by allograft function and proteinuria [19]. It is also advocated that the previously reported elevation of Lp(a) in cyclosporine-treated patients compared with azathioprine treatment [20] is caused by an inhibitory effect of azathioprine on Lp(a) metabolism [19].

Several large studies with long follow-up before the statin era (see below) accounted for independent association between lipid abnormalities, CVD, and mortality. For example, Kasiske found that hypercholesterolemia correlated with posttransplant vascular disease [21]. In a subsequent study, however, only HDL levels among lipid variables were independently associated with IHD [22]. Still, the risk for major IHD after the first year was increased twofold for patients with serum cholesterol >200 mg/dL or triglycerides >350 mg/dL [9]. Aker found a relative risk of 2.3 for post-transplant CVD associated with LDL cholesterol >180 mg/dL [23]. Aakhus reported independent association between IHD and total cholesterol [7]. Roodnatt showed in a retrospective study with over five years of follow-up that serum total cholesterol at one year was a significant independent predictor influencing all end points, including patient survival [24].

So far, there is no evidence that lipid lowering reduces the burden of CVD in RTRs. Several options are available for intervention. Tailoring immunosuppression with corticosteroid or cyclosporine withdrawal or avoidance and treatment with HMG-CoA reductase inhibitors (statins) will improve lipid abnormalities [12, 16]. Statins are widely used and their effects beyond lowering total and LDL cholesterol levels nominate them as an attractive alternative. Results of an ongoing, large, controlled fluvastatin trial are awaited.

**THE DIABETIC TRANSPLANT RECIPIENT**

Diabetes is the most common disease leading to ESRD in all Western countries. Diabetic nephropathy is associated with excess CVD morbidity and mortality at all stages of the disease. Diabetic patients manifest the highest mortality rate of any group of ESRD patients. Among patients starting dialysis, diabetics present more often with clinically diagnosed IHD [25]. Even in asymptomatic diabetic transplant candidates, coronary angiography can reveal coronary artery stenosis >50% in more than half of them [26]. Importantly, a pathologic coronary angiography may predict major adverse cardiovascular events after transplantation [26]. The survival benefit of renal transplantation over dialysis is especially valid for diabetic transplant recipients [1]. Therefore, it is advocated that renal transplantation should be the first therapeutic choice for all suitable diabetic ESRD patients. Diabetic RTRs are, however, at further increased CVD risk compared with non-diabetics. For example, Lindholm reported a twofold higher risk of death from IHD in diabetic RTRs compared with non-diabetics (25% vs. 11.4%) [3]. Arend found a 2.9 relative risk of mortality after the first year in diabetics [2]. Registry data from the United States account also for more than two-fold
higher than average risk of death from CVD in diabetic RTRs [5]. Aker reported a 4.3 times increased risk of post-transplant CVD in diabetics. [23]. Kasiske found IHD in 24% of diabetics versus 12% of non-diabetics [7]. In Kasiske’s study, diabetic RTRs had a more than threefold increased risk for IHD and for cerebrovascular disease and a 28-fold risk for peripheral vascular disease [22]. The relative risk for IHD associated with diabetes was three- to five-fold increased in a subsequent study [9]. Importantly, recent reports indicate that simultaneous pancreas-kidney transplantation reduces excess mortality in type 1 diabetic RTRs [27–29]. In addition, CVD mortality and left ventricular function will improve after successful pancreas transplantation [29]. Restoring normoglycemia may be the most significant factor for improved outcomes.

POST-TRANSPLANT HYPERTENSION

Hypertension is one of the most powerful predictors for CVD in the general population and is frequently associated with other CVD risk factors. Patients with renal disease have 60–100% prevalence of hypertension [10]. Pretransplant hypertension is a strong predictor of post-transplant hypertension. Several other contributory factors are recognized [30]. Genetic factors may also have an impact [31]. The prevalence increased from 50% to 70–90% in the cyclosporine era [30, 32]. Corticosteroids account for 15% of it [33], and steroid withdrawal ameliorates hypertension [16]. Tacrolimus and cyclosporine seem to have similar adverse impact on blood pressure in RTRs [16]. Ambulatory blood pressure monitoring may reveal a disturbed diurnal variation (non-dipper pattern), which was found to occur in 94.5% of patients with chronic allograft nephropathy [34]. Post-transplant hypertension may be associated with hyperlipidemia, IHD, and allograft failure and is also a significant independent risk factor for CVD [7].

Treatment of hypertension should be aggressive with target blood pressure below 130/80 [10, 30]. Several studies have shown that CCBs may protect from cyclosporine nephrotoxicity [30]. On the other hand, one recent study found adverse impact on IHD risk of dihydropyridine CCBs [9]. Patients with proteinuria would benefit more by treatment with angiotensin-converting enzyme inhibitors (ACE-Is) or angiotensin receptor antagonists. ACE-Is may have additional beneficial effects by reducing post-transplant erythrocytosis. The cardioprotective properties of β-blockers should be weighed against possible adverse metabolic consequences [30].

METABOLIC RISK FACTOR SYNDROME

Features of the metabolic risk factor syndrome [35] with obesity, hypertension, insulin resistance/impaired glucose tolerance/diabetes, lipid abnormalities with hypertriglyceridemia and low HDL cholesterol levels, and defect fibrinolysis have strong correlation with atherosclerotic vascular disease in the general population. Insulin resistance and similar lipid abnormalities are present in renal failure. After transplantation, immunosuppressive therapy, in particular corticosteroids, may further aggravate these metabolic abnormalities.

Obesity

Obesity has long been recognized as a significant risk factor for CVD in the general population, mainly from induction of other risk factors such as hypertension, insulin resistance, and associated metabolic abnormalities [35]. Few ESRD patients are obese; the pretransplant frequency is 14–26% depending on definition [32, 23, 36]. Weight gain of more than 10% after transplantation occurs in almost two thirds of patients, is influenced by demographic factors, and associated with increase in both serum cholesterol and triglyceride levels [36]. The prevalence of obesity is between 28% and 48% 1–2 years after transplantation [23, 32, 36]. Obese RTRs are at increased risk of adverse outcomes. Postoperative complications are more common, and the risk to develop post-transplant diabetes mellitus (PTDM) is increased (12% vs. 2%) [37]. Obesity with body mass index (BMI) >30 kg/m² was also found to be associated with reduced patient survival and increased prevalence of IHD [37]. Moderate obesity (BMI >25 kg/m²) was also associated with a 2–3 fold increased risk of CVD [23] and a twofold increased risk for graft loss and death [38].

Impaired glucose tolerance (IGT) and PTDM

The diabetogenic effect of corticosteroid therapy is well established and is principally mediated by induction of insulin resistance [39]. Both cyclosporine and tacrolimus have adverse impact on insulin and glucose metabolism, with tacrolimus possibly being more diabetogenic, especially in certain patient populations [16, 39]. Insulin resistance and impaired glucose tolerance (IGT) is often present in RTRs [32, 40]. When insulin resistance is associated with impaired insulin secretion, PTDM will develop [40]. At 10 weeks after transplantation 52% of patients had glucose intolerance, including those with PTDM [40]. Age, heredity, corticosteroid dose, hypertriglyceridemia, elevated apoB and 2-hour insulin levels were all independently associated with these abnormalities, thus linking IGT and PTDM to the metabolic syndrome [40].

The frequency of PTDM in the cyclosporine era is 8–18%, with manifestation most frequently reported during the first 3 post-transplant months [39]. According to a recent report, the risk of PTDM may increase continuously with time after transplantation, and the prevalence has almost doubled since 1995 (5.9 vs. 10.5% at
It is estimated that steroids are responsible for 10%, and cyclosporine for an additional 5% [33]. Similar to IGT, older age, higher steroid doses, and a positive family history of diabetes are established risk factors for PTDM [39]. PTDM is associated with a more than twofold increased relative risk of IHD, and also with higher post-transplant cholesterol and triglyceride and lower HDL levels, further major predictors of IHD [22]. The adverse impact of PTDM on patient survival is, however, not equally evident at different centers. For example, Miles reported 12-year survival of PTDM patients similar to controls (71% vs. 74%) [42]. Revanur found inferior 10-year survival of PTDM patients compared with non-diabetics (49% vs. 75%) [43]. Only patients younger than 55 years accounted for this survival difference, and for them, PTDM was associated with 2.54 times higher risk of death [43].

Similar to lipid abnormalities, management of PTDM may include modification of immunosuppression with successive withdrawal or avoidance of corticosteroids and calcineurin inhibitors, strategies with well-documented beneficial metabolic consequences [39]. Achievement of optimal metabolic control with oral hypoglycemic agents and if necessary with insulin therapy, albeit not documented in RTR, is probably as important as in non-transplanted diabetic patients [39].

**Fibrinolysis**

Impaired fibrinolysis is associated with increased cardiovascular morbidity. PAI-1 is the specific inhibitor of the fibrinolytic system, and elevated levels of PAI-1 are associated with impaired fibrinolysis, increased risk of thrombosis, and CVD in the general population. Elevated PAI-1 levels are coupled with other features of the metabolic risk factor syndrome such as obesity, hypertriglyceridemia, and hyperinsulinemia and non-insulin dependent diabetes, thus linking defective fibrinolysis to the insulin resistance syndrome. Impaired fibrinolysis and elevated PAI-1 activity are frequently observed with corticosteroids [44] and cyclosporine [45] are suggested contributors. Hypercholesterolemia, obesity, and steroid-induced diabetes could be identified as risk factors for elevated plasma PAI-1 activity in cyclosporine-treated patients [45]. Conversion from cyclosporine to azathioprine as well as steroid withdrawal resulted in improved fibrinolysis and decrease in PAI-1 levels [46, 47]. Presence of impaired fibrinolysis together with all other features of the metabolic syndrome six months after transplantation was associated with poor outcome [32].

**SMOKING**

Smoking increases the risk for CVD in the general population. Several studies demonstrated increased risk of CVD and mortality in kidney transplanted smokers [2, 23, 48, 49]. Smoking had similar negative impact on patient survival as diabetes [48]. Heavy smokers (>25 pack-years) at the time of transplantation had 1.42 relative risk for post-transplant mortality and 2.14 relative risk for CVD [49]. There was no adverse effect of smoking among patients who quit more than 5 years before transplantation [49]. Smoking cessation is highly recommended for patients with renal disease.

**RENAL DISEASE/UREMIA-ASSOCIATED RISK FACTORS**

**Homocysteine**

Moderate hyperhomocysteinemia is an independent predictor of atherosclerotic vascular disease in the general population. In renal failure, hyperhomocysteinemia develops in parallel with the degree of decreasing GFR [50]. After renal transplantation, total homocysteine (tHcy) levels decrease but do not normalize [51]. Whether cyclosporine therapy contributes to elevated post-transplant tHcy levels is controversial [50-53]. Tacrolimus-treated patients were not found to have independent difference in tHcy levels compared with those treated with cyclosporine [54]. Association of elevated PAI-1 activity and homocysteine levels is of interest, linking hyperhomocysteinemia to defect fibrinolysis and the metabolic syndrome [55]. Increased tHcy levels are present in 5,10-methylenetetrahydrofolate reductase (MTHFR) gene polymorphism (677 C > T). However, the TT genotype is not over-represented in RTRs [55].

Hyperhomocysteinemia is linked to an almost three-fold risk of de novo or recurrent CVD in ESRD and suggested as a risk factor for CVD in RTRs by several studies [56]. Recently, tHcy was found to be associated with a relative risk of 1.06 for CVD [52]. Notably, s-creatinine levels were also independently related to CVD events (1.34 relative risk) and were also the major determinants of tHcy levels. The importance of serum creatinine as the major independent determinant of plasma tHcy level is underlined by a recent study [53]. Two other studies could not find any association between hyperhomocysteinemia and patient or graft survival [57, 58].

Folic acid supplementation in pharmacological dose, preferably complemented with B6 and B12 vitamins, can effectively reduce the hyperhomocysteinemia of RTRs [54, 56]. This decrease seems to be influenced by the MTHFR genotype, as patients with the 677TT genotype reduce tHcy levels most. Furthermore, elevated PAI-1 levels also decreased after 2 months of therapy [55]. The potential beneficial effect of vitamin supplementation on patient and/or graft survival and on CVD events in RTRs remains to be demonstrated.
**Proteinuria**

Proteinuria is a risk factor not only for progressive renal disease but also for CVD [8]. In RTRs, both early and late proteinuria predicts adverse outcome [59, 60]. Proteinuria one year after transplantation occurred during a follow-up of at least five years associated with twofold increased risk of death [60].

**Left ventricular hypertrophy and dysfunction**

LVH is present in the majority of patients starting renal replacement therapy and is associated with adverse outcome. Risk factors for LVH include anemia, hypertension, hypoalbuminemia, ischemic heart disease, and volume overload. [10, 61]. Time on dialysis may also influence LVH [62]. Renal transplantation leads to regression of LVH paralleling blood pressure improvement [61]. LVH regression was found to continue during the first two years, and it remained unchanged up to four years after renal transplantation [63]. Older age and hypertension may retard this process [63]. The ACE-DD genotype also favors LVH in RTRs, and these patients will, as expected, benefit more from ACE-inhibitors, independent of blood pressure control [64]. Nevertheless, in a double-blind randomized trial with equally well-controlled blood pressure, the effect on LVH reduction was similar in hypertensive RTRs treated with the ACE-I lisinopril or a CCB, controlled release nifedipine [65]. The presence of LVH, as well as ventricular dilatation and poor systolic function before transplantation, predicted increased mortality after renal transplantation during a median follow up of 7.5 years, while other, traditional risk factors such as hypertension, hyperlipidemia and smoking did not. Subsequently, on echocardiography performed 4 months after transplantation, only LVH provided a stronger association with adverse outcome during follow-up [66]. Prevention of the development of LVH by optimal treatment of hypertension, preferably with ACE inhibitors throughout the course of renal disease [61], control of renal anemia and volume overload may be beneficial for reducing CVD also after renal transplantation.

**Time on dialysis**

CVD has a propensity to accelerated progression during the years on dialysis, particularly in diabetic patients. Pretransplant vascular disease is one of the strongest predictors of post-transplant CVD [21]. Thus, it could be expected that the length of prior dialysis therapy would also have a negative impact on CVD morbidity and mortality after renal transplantation. Indeed, time on dialysis had a strong negative influence on patient survival after transplantation in some [62] but not all studies [2]. Registry data reveal, however, that waiting time, in a dose-dependent manner, is a strong independent risk factor for increased mortality after transplantation in the United States [67].

**SUMMARY**

Cardiovascular disease after renal transplantation is a major challenge. As the accelerated atherosclerotic vascular disease starts during the early phase of chronic renal disease and has a propensity to progress rapidly during dialysis therapy, efforts have to concentrate on reducing CVD risk factors at all stages of renal disease. During the past decade, substantial improvement of patient survival after renal transplantation was observed [5, 6]. To further improve the outcome for RTRs, awareness of the potential hazards associated with CVD risk factors and therapeutic measures to reduce modifiable risk factors, and thereby the incidence and consequences of CVD, are advocated.

**REFERENCES**

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