ATHEROSCLEROSIS AND INFLAMMATORY STATUS IN CHRONIC KIDNEY DISEASE PATIENTS AFTER RENAL TRANSPLANTATION: WHERE ARE WE NOW?

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ABSTRACT

Cardiovascular diseases are the most common cause of mortality and morbidity in patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD), receiving haemodialysis, peritoneal dialysis, and renal transplantation (Rtx). Estimated glomerular filtration rate (eGFR) places Rtx patients in one of the stages of CKD. Therefore, Rtx patients might be considered a subset of CKD patients. Besides the traditional risk factors of hypertension, diabetes, and dyslipidaemia, advanced-age novel risk factors such as endothelial dysfunction, vascular calcification, and increased chronic low-grade inflammation are highly prevalent and seem to play a more important role for vascular disease in CKD and Rtx patients compared to the general population. The role of Rtx in terms of atherogenesis and chronic ongoing low-grade inflammation is still unclear. To date, in the literature, the data are scant regarding the relationship between atherosclerosis, chronic inflammation, and cardiovascular events in Rtx patients with well-functioning kidneys. This review will discuss classical and recent epidemiological, pathophysiological, and clinical aspects of atherosclerosis and inflammation in Rtx patients.

Keywords: Atherosclerosis, inflammation, renal transplantation.

INTRODUCTION

Cardiovascular diseases (CVDs) are the most common cause of mortality and morbidity in patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD) receiving haemodialysis (HD), peritoneal dialysis (PD), and renal transplantation (Rtx). Cardiovascular (CV) risk is increased even in the early stages of CKD and this heightened risk is also found to be ongoing in ESRD patients who received Rtx.¹² Transplant recipients have a lower risk of fatal and non-fatal CV events compared with wait-listed patients on dialysis;³⁴ however, these patients have a much higher risk compared with the general population.⁵ 50-60% of post-Rtx deaths were found to be associated with CVD, with an incidence of ischaemic heart disease of approximately one per 100 person-years at risk.⁶ CVD is the most common cause of death with graft function after transplant, and accounts for 30% of graft loss from death overall, with the greatest rates early after Rtx.⁷ Rtx is accepted as the optimal renal replacement therapy method; however, CV mortality remains three-to-five times higher in this patient population compared to general population.⁸ Despite the improvement in kidney functions of this population after Rtx, estimated glomerular filtration rate (eGFR) places them in one of the stages of CKD.
Besides traditional risk factors including hypertension, diabetes, dyslipidaemia, advanced age, and left ventricular hypertrophy (LVH), novel risk factors such as endothelial dysfunction (ED), vascular calcification (VC), oxidative stress, and inflammation are highly prevalent and seem to play a more important role for vascular disease in renal patients compared to healthy subjects.\textsuperscript{3-12} CKD is now recognised as an independent risk factor for coronary artery disease (CAD) in community-based studies as well as in high CV-risk populations. In community-based studies, decreased glomerular filtration rate (GFR) and proteinuria were both found to be independently associated with CAD.\textsuperscript{13-15} Growing evidence suggests that a gradual fall in GFR is also independently associated with CV events in patients with preexisting CVD.\textsuperscript{16-19} In addition, several studies demonstrated that systemic, persistent inflammation could be the main factor responsible for the increased risk in this population, regardless of the renal replacement therapy.\textsuperscript{20}

The role of Rtx in terms of atherogenesis and chronic, ongoing, low-grade inflammation is still unclear. To date, in the literature, the data are scant regarding the relationship between atherosclerosis, chronic inflammation, and CV events in Rtx patients with well-functioning kidneys. This review will discuss classical and recent epidemiological, pathophysiological, and clinical aspects of atherosclerosis and inflammation in Rtx patients. Treatment of atherosclerosis and inflammation in patients with Rtx is beyond the scope of this review.

**ATHEROSCLEROSIS IN CKD AND RTX PATIENTS**

**Pathophysiology**

Atherosclerosis is a condition characterised by formation of plaques (also referred to as atheroma) on the intima layer of vessels. According to the American Heart Association (AHA) guidelines, coronary atherosclerotic plaques constitute most of the CV diseases in the general population.\textsuperscript{24} However, the pathophysiology of vascular disease in CKD and Rtx is poorly understood and quite different from that related to atherosclerosis in the general population.\textsuperscript{25} Besides traditional risk factors including hypertension, diabetes, and dyslipidaemia, advanced-age novel risk factors such as ED and CKD-mineral bone disorders (CKD-MBD), abnormalities including hyperphosphataemia, hyperparathyroidism, and vascular-valvular calcification, increased oxidative stress, and chronic low-grade inflammation are highly prevalent and seem to play a more important role for vascular disease commonly seen in CKD and Rtx patients compared to healthy subjects.\textsuperscript{9-12,26} In theory, the first step of this process is triggered by ED; however, in recent years several studies have demonstrated that systemic, persistent inflammation could be the main factor responsible for the increased risk in these patients regardless of the renal replacement therapy.\textsuperscript{20} To prove this hypothesis, several biomarkers, including C-reactive protein (CRP), interleukin (IL)-1\textbeta, IL-6, and tumour necrosis factor-\greekalpha (TNF-\greekalpha), were considered in CVD and CKD populations including Rtx patients.\textsuperscript{20,26,27} This issue will be addressed below.

Besides the factors mentioned above, the reasons why CKD patients are prone to worse
CV outcomes and why these anticipated events remain after Rtx are still unclear. In the general population, many patients with CAD develop coronary collateral circulation to overcome obstruction of the atherosclerotic coronary arteries. Charytan et al. hypothesised that CKD and Rtx patients might have less collateral blood supply to an ischaemic area of the myocardium and this hypothesis might partially explain why CKD and Rtx patients have worse CV outcomes and death. However, this study has failed to prove this hypothesis because both CKD patients and subjects without CKD had similar culprit artery collateral supply (25% versus 27.2%, respectively, p=0.76).

**Traditional Risk Factors**

Traditional risk factors for coronary heart disease after Rtx were investigated in a report of 403 patients who received 464 kidney transplants during a 10-year period. New atherosclerotic complications developed in 16% of Rtx patients. After accounting for pre-Rtx vascular disease, multivariate analysis revealed that risk factors including advanced age, diabetes mellitus, male sex, smoking, hypertension, and hypercholesterolaemia are independently associated with post-transplant atherosclerotic CVD.

Both pre-transplant diabetes and new-onset diabetes after transplant (NODAT) are closely associated with the increased risk of post-Rtx CV complications such as myocardial infarction (MI) and heart failure. Medications that contribute to NODAT include glucocorticoids, calcineurin inhibitors, and mammalian target of rapamycin (mTOR) inhibitors.

Dyslipidaemia has been established as a classic risk factor for CVD in the general population and in CKD patients receiving HD, PD, and Rtx. Large-scale observational studies have confirmed that dyslipidaemia may actively participate in the pathogenesis of atherosclerosis in the general population. Additionally, it has been well recognised that CKD patients (including Rtx patients) exhibit significant alterations in lipoprotein metabolism, which may result in the development of severe dyslipidaemia in this population.

Previous studies demonstrated that hypertriglyceridaemia might be the earliest laboratory finding among the other lipid abnormalities even in patients who have slightly elevated creatinine levels. In contrast, high density lipoprotein (HDL) cholesterol was found to be inversely related to the CV risk in non-CKD population. HDL is not only a key player in reverse cholesterol transport but also has the ability to protect low-density lipoprotein (LDL) against oxidation. Uraemic patients usually have increased concentrations of triglyceride-rich lipoproteins and reduced serum levels of HDL-cholesterol. In addition to HDL and oxidised LDL, carbamylated LDL is proposed to cause endothelial injury and progression of atherosclerosis in patients with kidney disease. However, LDL-cholesterol values were found to be within normal limits or reduced in this population.

There has been a strong relation between CKD and hypertension whereby each can cause or aggravate the other. Control of blood pressure (BP) is fundamental to avoid the progression of CKD, hence several clinical practice guidelines have been published on this topic by many authorities over the last 10 years. Additionally, in hypertensive CKD patients, inappropriate LVH may occur, which can be estimated by the ratio of observed to predicted left ventricular mass (LVM). Recently, the ratio of observed to predicted LVM was found to be independently associated with increased CV events in patients with CKD Stages 3-5.

Since hypertension in patients with CKD contributes to the particularly high risk of CV morbidity and mortality, ambulatory blood pressure measurement (ABPM) is one of the important diagnostic tools, especially in patients with poorly controlled hypertension. Andersen et al. showed that, approximately 30% of CKD patients had office BP measurements higher than ABPM, whereas 28% of the patients had office BP measurements below ABPM. ABPM showed a stronger correlation with LVM index and proteinuria than single casual office BP measurements in patients with CKD and in the general population. A study comparing the prognostic value of office BP and home BP monitoring showed that home measurements were superior to office BP and predicted ESRD independently of other risk factors.

Post-transplant hypertension is also a risk factor for CVD and chronic allograft dysfunction. Among the causes of increased BP in Rtx patients are: reduced vascular compliance, autonomic neuropathy, latent over hydration, use of erythropoietin, corticosteroids, and cyclosporine.
A.51,52 ABPM may be more informative regarding the intensity of BP elevation than clinical measurements following Rtx.53 In addition, recently, we demonstrated that prevalence of masked hypertension (MHT) is in Rtx patients.54 According to our study results, Rtx from a deceased donor may be a predictor of MHT. The prevalence of MHT may help to explain high rate of CV events in Rtx patients. Therefore, routine application of ABPM in patients with Rtx may be plausible, particularly in patients with deceased donor type.

Recently, Kidney Disease Improving Global Outcomes (KDIGO) published a guideline regarding the management of BP in CKD.55 According to this report they recommend that non-diabetic, adult CKD patients who have urine albumin excretion (UAE) ≤30 mg/24 hours and office BP >140/90 mmHg should be treated with antihypertensive agents, especially with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. They also suggested that BP target should be ≤130/80 mmHg in those who had UAE of 30-300 mg/24 hours and UAE ≥300 mg/24 hours.

**Novel (Non-Traditional) Risk Factors**

**Inflammation**

Inflammation seen after Rtx has complexity including innate and acquired immunity. Macrophages and neutrophils play an important role in the pathogenesis of inflammation and acute and chronic allograft rejection.56 However, ongoing inflammation in Rtx patients is much less intense compared to CKD and ESRD patients. In recent years, researchers analysed a large panel of biomarkers to fully characterise the relationship between inflammation and CVD, including CRP, IL-1β, IL-6, and TNF-α.20,26,27,57 In addition, several interesting new biomarkers were considered to better describe inflammation in Rtx patients, a CKD population with a particular profile, taking into account the allograft and the immunosuppressive therapy role. In this regard, neutrophil-to-lymphocyte ratio (NLR) is a potential marker for inflammation in cardiac and non-cardiac disorders58-60 that was also shown to be a predictor of long-term mortality in patients who underwent percutaneous coronary intervention.61 Our group demonstrated that NLR could predict inflammation in ESRD patients and in Rtx patients.57,62 However, NLR in transplant recipients may be affected by immunosuppressive medications regardless of the kidney graft function because this relationship might be biased. In the following years, like NLR before it, platelet to lymphocyte ratio (PLR) was found to be closely related to CV events in both general and CKD population.63-65

Recently, a novel marker - the soluble TNF-like weak inducer of apoptosis (sTWEAK, TNFSF12) - was introduced as a TNF-related cytokine in various inflammatory and non-inflammatory disorders.66 To date, a transmembrane protein (fibroblast growth factor-inducible 14 [Fn14]) and a scavenger receptor (CD163) were discovered as receptors of sTWEAK.57,68 The first description of sTWEAK in the kidney was reported by Justo et al. in a mouse model of folate-induced acute kidney injury. Binding of sTWEAK to Fn14 mediates multiple effects including: cellular growth, proliferation, migration, differentiation, apoptosis, angiogenesis, fibrogenesis, and inflammation.70 In the following years, Yilmaz et al.71 demonstrated that a decline in eGFR was accompanied by a gradual reduction in sTWEAK in CKD patients. The same group also showed that ED and decreased sTWEAK were independently associated with CV outcomes in pre-dialytic CKD patients.72 Moreover, treatment of type 1 hypertensive diabetic CKD with amlodipin and/or valsartan was found to be effective in terms of ED and normalisation of sTWEAK.73 A study by Turkmen et al.74 demonstrated that Rtx patients had lower sTWEAK levels compared to healthy subjects. In this study, median values of sTWEAK levels of Rtx patients were found to be higher compared to CKD patients in the cohorts of Yilmaz et al.72 and Carrero et al. (388.97 pg/mL versus 245.5 pg/mL and 208 pg/mL, respectively). Turkmen et al.74 also tested the relation between sTWEAK and kidney function in Rtx patients. After the classification of Rtx patients according to their eGFR, they found that sTWEAK levels were significantly decreased when eGFR values were decreased. These findings were similar to those obtained from the study by Yilmaz et al.71 and Gungor et al.76 We hypothesised that the decrement of sTWEAK among eGFR groups in Rtx patients might be associated with ongoing inflammation in this population. For a better understanding, we illustrated this relationship in Figure 1.

**VC IN CKD AND RTX PATIENTS**

VC is very common and is becoming increasingly prevalent with the worsening of kidney function...
in patients with CKD and Rtx. The importance of this process has been demonstrated by the tight relationship between VC and increased cardiac mortality in these populations.\textsuperscript{77} The haemodynamic consequences of VC include a decrease in coronary microcirculation and arterial elasticity, an increase in pulse wave velocity, and increased LVH.\textsuperscript{24,25} VC may develop in the intimal or the medial layer of the vessel wall. The latter is also referred to as ‘Monckeberg’s sclerosis’ and is much more common in patients with CKD compared to the general population.\textsuperscript{78} The main differences between these two types of VC are as follows: i) intimal calcification is highly associated with inflammation and focal occlusion secondary to the plaque formation; however, medial calcification is characterised by diffuse pipe type calcification of muscular arteries; ii) intimal calcification is commonly seen in coronary, carotid arteries, and aorta, whereas medial calcification is commonly observed in tibial and femoral arteries.\textsuperscript{79-81}

Longitudinal studies of VC in Rtx patients are few and small, with short follow-up. Recently, Maréchal et al.\textsuperscript{82} assessed the evolution of coronary artery and thoracic aorta calcification and their determinants in a cohort of 281 prevalent Rtx patients. They found that VC progression was substantial within 4 years in prevalent Rtx patients and was associated with several traditional and non-traditional CV risk factors. According to the study results, higher baseline coronary artery calcification score (CACS), history of CV event, usage of statins, and lower 25-hydroxyvitamin D(3) level were independent determinants of CAC progression; higher baseline aorta calcification score, higher pulse pressure, use of a statin, older age, higher serum phosphate level, use of aspirin, and male sex were independent determinants of aorta calcification progression. They also concluded that significant regression of CAC or aorta calcification was not observed in Rtx patients.

Relation of VC with Malnutrition, Inflammation, and Atherosclerosis

Despite beneficial effects of Rtx, this procedure could not reverse increased CV morbidity and mortality in ESRD patients. The question of why there are worse outcomes in this population might be answered by the association with a vicious cycle named malnutrition-inflammation-atherosclerosis/
calcification (MIAC) syndrome. MIAC syndrome has been defined as the interaction between increased levels of proinflammatory cytokines, malnutrition, and atherosclerosis/calcification in ESRD patients.\textsuperscript{63,84} Stenvinkel et al.\textsuperscript{85} hypothesised that malnutrition, inflammation, and atherosclerosis cause a vicious cycle, and that proinflammatory cytokines play a central part in this process. The presence of MIAC components was found to be associated with increased mortality and morbidity in ESRD patients receiving PD\textsuperscript{85} or HD.\textsuperscript{86} The CAC is a part of the extended state of VC, which can be detected even in the early decades of patients with ESRD;\textsuperscript{27,80} and reflects the severity of atherosclerotic vascular disease and predicts CV events.\textsuperscript{87,88} Wang et al.\textsuperscript{84} showed an important association between MIAC syndrome and valvular and vascular calcification in PD patients. In a recent study, the correlation of CACS with coronary flow velocity reserve (CFVR) was investigated in HD patients.\textsuperscript{89} According to the results of this study, HD patients with CACS >10 had a significantly lower CFVR, and the functional deterioration of coronary arteries started from low levels of CACS.

Taken together, these traditional and non-traditional risk factors, including chronic low-grade inflammation, vascular calcification, and malnutrition, might contribute to ongoing CVD and the markedly increased mortality in patients with Rtx.

### CLINICAL STUDIES OF ATHEROSCLEROTIC CVD

Baber et al.\textsuperscript{90} aimed to determine the impact of CKD on atherosclerotic plaque composition, morphology, and outcomes in patients with CAD. The authors demonstrated that CKD patients had more extensive and severe atherosclerotic plaques composed of greater necrotic core and less fibrotic tissue. They also concluded that in the following 3-years, CKD patients had a significantly higher rate of acute MI, cardiac arrest, and death compared to patients without CKD, although there was no significant difference in the rates of events adjudicated to nonculprit lesions. Similarly, Kawai et al.\textsuperscript{91} demonstrated that the prevalence of severe coronary artery stenosis (≥70% of luminal diameter), defined by 320-row area computed tomography, was significantly higher in 131 patients with mild CKD (eGFR≥60 mL/min) compared with patients without CKD (35.1% versus 19.4%, p=0.0003, respectively), although there were no significant differences in the prevalence of high-risk plaque (13.0% versus 9.8%, p=0.3189, respectively).

In a substudy of the Acute Catheterisation and Urgent Intervention Triage strategy (ACUITY) trial, Acharji et al.\textsuperscript{92} aimed to show the prognostic value of baseline troponin levels of 2,179 CKD patients with moderate and high-risk of ACS. Of 2,179 CKD patients, 1,291 had elevated baseline troponin (59.2%). CKD patients with higher baseline serum troponin levels had significantly higher rates of death, MI or unplanned revascularisation at 30 days and 1 year compared with CKD patients without baseline troponin elevation. Another important result of this study confers that baseline elevation of troponin independently predicts death or MI at 30 days and 1 year (HR=2.05 [1.48-2.83], p<0.0001 and HR=1.72 [1.36-2.17], p<0.0001, respectively). However, diagnosis of ACS in the patients with CKD based on troponin levels should be interpreted cautiously.

Among all dialysis patients, a cardiac mortality has been estimated as 40%. Additionally, this high rate reaches up to 50% in diabetic ESRD patients without any ACS symptoms. Accurate diagnosis of ACS is quite different in this population. In a study of 274,777 subjects (CKD, non-CKD, and patients receiving dialysis) enrolled from the US Renal Data System (USRDS) and the Third National Registry of Myocardial Infarction (NRM\textsuperscript{3}), outcomes were reported for several subgroups, including patients with advanced CKD (baseline serum creatinine ≥2.5 mg/dL), ESRD patients receiving dialysis, and patients without CKD.\textsuperscript{93} On admission, chest pain, ST elevation, and diagnosis other than ACS were seen in 40.4%, 15.9%, and 44% of patients with advanced CKD; 41.1%, 17.6%, and 47.7% of ESRD patients receiving dialysis; and 61.6%, 32.5%, and 25.8% of patients without CKD, respectively. In addition, mortality rates, unexpected cardiac arrest, and CHF were seen in 23%, 8.9%, and 41% of patients with advanced CKD; 21.7%, 12.3%, and 25.8% of ESRD patients receiving dialysis; and 12.6%, 6%, and 21.1% of patients without CKD, respectively (p>0.0001 for all comparisons).

Despite many studies on CKD patients, there has been limited clinical data on Rtx patients regarding CV morbidity and mortality. A retrospective study based upon the United States Renal Data System (USRDS) evaluated the clinical correlates of post-transplant MI. Among nearly 36,000 patients, the incidence of MI at 6, 12, and 36 months was
4.3%, 5.2%, and 11.1%, respectively. The principal risk factors were increased age, recipient of kidneys from older and deceased donors, delayed allograft function, and the presence of pretransplant disease including diabetes mellitus, angina pectoris, peripheral vascular disease, and MI. The diagnosis of post-transplant diabetes and the development of allograft failure were also significantly associated with the development of a MI. In a study of 53,297 patients, a markedly increased risk of acute MI was observed early after Rtx, <3 months post-surgery. Compared with waitlist patients, the risk also varied by recipients of a deceased donor kidney (RR 3.57, 95% CI 3.21-3.96) and living donor kidney (RR 2.81, 95% CI 2.31-3.42).

Circulating fibroblast growth factor 23 (FGF23) was found to be closely associated with adverse CV outcomes in CKD. Whether FGF23 predicts CV mortality after Rtx, independent of measures of mineral metabolism and CV risk factors, was unknown. Baia et al. demonstrated that plasma FGF23 was independently associated with CV and all-cause mortality after Rtx. The association remained significant after adjustment for measures of mineral metabolism and CV risk factors.

CONCLUSION

The risk of atherosclerosis is unexpectedly high in patients with CKD and Rtx. To date, we know more about the pathogenesis of CAD in these populations; however, much remains unknown. Further experimental and randomised controlled clinical studies are needed to define the exact pathophysiological and clinical aspects of atherosclerosis especially in the Rtx population.

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