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.[1,2] Transplant recipients have a lower risk of fatal and non-fatal CV events compared with wait-listed patients on dialysis;[3,4] 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.[9-12] 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.[13-15] Growing evidence suggests that a gradual fall in GFR is also independently associated with CV events in patients with preexisting CVD.[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.[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.

EPIDEMIOLOGY

Epidemiological studies have repeatedly shown the close relationship between CV events and CKD. However, there have been no large-scale population-based studies regarding CV events in Rtx patients. In this regard, population-based studies in CKD and ESRD patients might be fruitful to assess the CV risk of Rtx patients.

The largest population-based study demonstrated that a decline in GFR was the main independent risk factor for CV events - including hospitalisation secondary to peripheral artery disease (PAD), CAD, congestive heart failure (CHF), or stroke - even after the elimination of confounding risk factors, in more than 1.1 million adults.[21] Similar findings were also reported in a systematic review considering approximately 1.4 million adults from 42 different cohorts.[22] According to this review's results, the risk of all-cause mortality was highest in patients with lowest baseline GFR and vice versa. The gradual fall of GFR was also found to be associated with a gradual increase of death.

CV risk is increased even in the early stages of CKD, particularly in the elderly and this risk remains after several years of Rtx. In a study including approximately 30,000 older CKD patients with estimated GFR of <90 mL/min/1.7m^2, the rate of mortality at 5 years was 19.5%, 24.3%, 45.7% in those with CKD Stage 2, 3, or 4, respectively.[23]

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.[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.[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.[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.[20] To prove this hypothesis, several biomarkers, including C-reactive protein (CRP), interleukin (IL)-1β, IL-6, and tumour necrosis factor-α (TNF-α), were considered in CVD and CKD populations including Rtx patients.[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.[28] 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.[29] 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.[3,8]

Dyslipidaemia has been established as a classic risk factor for CVD in the general population[30] and in CKD patients receiving HD, PD, and Rtx.[31] Large-scale observational studies have confirmed that dyslipidaemia may actively participate in the pathogenesis of atherosclerosis in the general population.[32] 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.[33]

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.[33,34] In contrast, high density lipoprotein (HDL) cholesterol was found to be inversely related to the CV risk in non-CKD population.[35] 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.[36] However, LDL-cholesterol values were found to be within normal limits or reduced in this population.[37]

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.[38,39] 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.[40]

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.[41] Andersen et al.[42] 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[43] and proteinuria than single casual office BP measurements in patients with CKD[44] and in the general population.[45] 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.[46]

Post-transplant hypertension is also a risk factor for CVD and chronic allograft dysfunction.[47,48] Among the causes of increased BP in Rtx patients are: reduced vascular compliance,[49] autonomic neuropathy,[50] 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 prevalance 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 disorders[58-60] 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.[67,68] The first description of sTWEAK in the kidney was reported by Justo et al.[69] 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.[75] (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

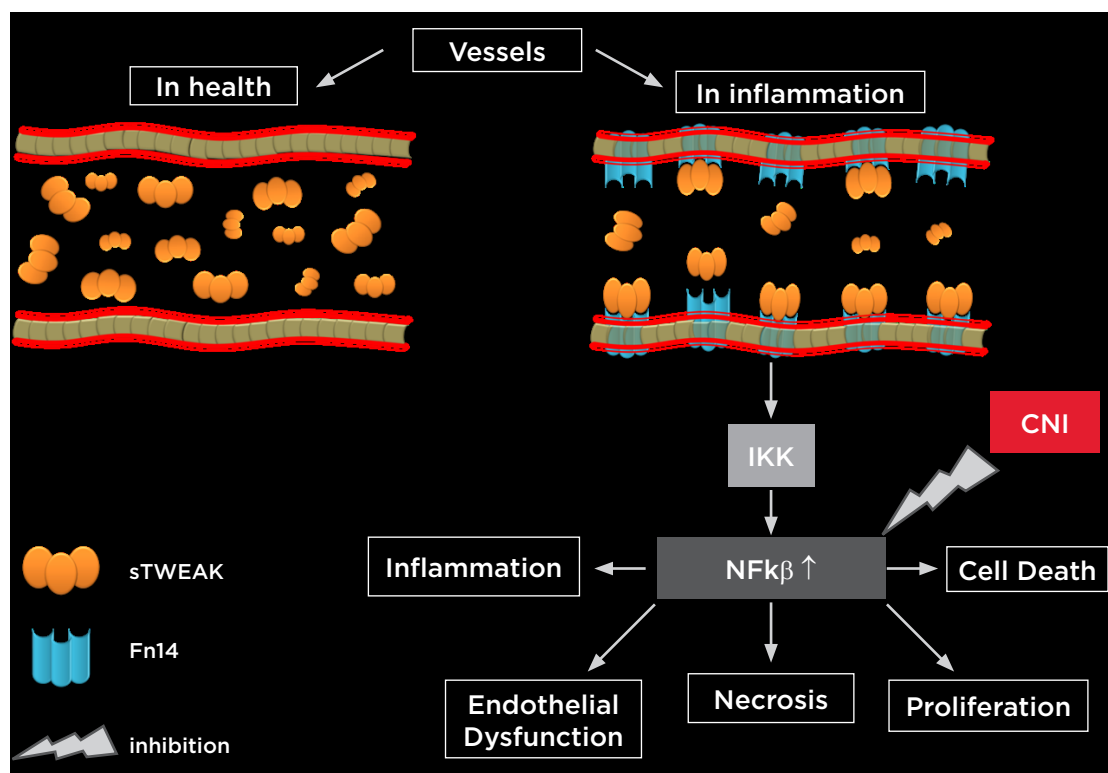VC is very common and is becoming increasingly prevalent with the worsening of kidney function

Figure 1: The relationship between sTWEAK and inflammation in renal transplant patients.
Fn14: fibroblast growth factor-inducible 14; IKK: I kappa kinase; CNI: calcineurin inhibitor; NFKβ: nuclear factor kappa-light-chain-enhancer of activated B cells.

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.[77] The haemodynamic consequences of VC include a decrease in coronary microcirculation and arterial elasticity, an increase in pulse wave velocity, and increased LVH.[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.[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.[79-81]

Longitudinal studies of VC in Rtx patients are few and small, with short follow-up. Recently, Maréchal et al.[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–atheroscleosis/

calcification (MIAC) syndrome. MIAC syndrome has been defined as the interaction between increased levels of proinflammatory cytokines, malnutrition, and atherosclerosis/calcification in ESRD patients.[83,84] Stenvinkel et al.[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[85] or HD.[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,[27,80] and reflects the severity of atherosclerotic vascular disease and predicts CV events.[87,88] Wang et al.[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.[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.[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.[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 prevalance 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.[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 (NRMI 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.[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 pre-transplant 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.[3] In a study of 53,297 patients, a markedly increased risk of acute MI was observed early after Rtx, <3 months post-surgery.[94] 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.[95] Whether FGF23 predicts CV mortality after Rtx, independent of measures of mineral metabolism and CV risk factors, was unknown. Baia et al.[96] 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.

REFERENCES

1. Morris ST et al. Endothelial dysfunction in renal transplant recipients maintained on cyclosporine. Kidney Int. 2000;57(3): 1100-6.

2. Vanholder R et al. Chronic kidney disease as cause of cardiovascular morbidity and mortality. Nephrol Dial Transplant. 2005;20(6):1048-56.

3. Lentine KL et al. Incidence and predictors of myocardial infarction after kidney transplantation. J Am Soc Nephrol. 2005;16(2):496-506.

4. Meier-Kriesche HU et al. Kidney transplantation halts cardiovascular disease progression in patients with end-stage renal disease. Am J Transplant. 2004;4(10):1662-8.

5. Jardine AG et al. Prevention of cardiovascular disease in adult recipients of kidney transplants. Lancet. 2011;378(9800):1419-27.

6. Ojo AO. Cardiovascular complications after renal transplantation and their prevention. Transplantation. 2006;82(5):603-11.

7. US Renal Data System. USRDS 2008 Annual Data Report: atlas of chronic kidney disease and end-stage renal disease in the united states. national institutes of health nio. 2008.

8. Lentine KL et al. Cardiovascular risk assessment among potential kidney transplant candidates: approaches and controversies. Am J Kidney Dis. 2010;55(1):152-67.

9. Parfrey PS et al. Outcome and risk factors for left ventricular disorders in chronic uraemia. Nephrol Dial Transplant. 1996;11(7):1277-85.

10. Cheung AK et al. Atherosclerotic cardiovascular disease risks in chronic hemodialysis patients. Kidney Int. 2000;58(1):353-62.

11. Muntner P et al. Traditional and nontraditional risk factors predict coronary heart disease in chronic kidney disease: results from the atherosclerosis risk in communities study. J Am Soc Nephrol. 2005;16(2):529-38.

12. Himmelfarb J et al. The elephant in uremia: oxidant stress as a unifying concept of cardiovascular disease in uremia. Kidney Int. 2002;62(5):1524-38.

13. Sarnak MJ et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on kidney in cardiovascular disease, high blood pressure research, clinical cardiology, and epidemiology and prevention. Circulation. 2003;108(17):2154-69.

14. Muntner P et al. Renal insufficiency and subsequent death resulting from cardiovascular disease in the United States. J Am Soc Nephrol. 2002;13(3): 745-53.

15. Foley RN et al. Chronic kidney disease and the risk for cardiovascular disease, renal replacement, and death in the United States Medicare population, 1998 to 1999. J Am Soc Nephrol. 2005;16(2):489-95.

16. Rahman M et al. Cardiovascular outcomes in high-risk hypertensive patients stratified by baseline glomerular filtration rate. Ann Intern Med. 2006;144(3):172-80.

17. van der Velde M et al. Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality. A collaborative meta-analysis of high-risk population cohorts. Kidney Int. 2011;79(12):1341-52.

18. Segura J et al. Development of chronic kidney disease and cardiovascular prognosis in essential hypertensive patients. J Am Soc Nephrol. 2004;15(6):1616-22.

19. Knobler H et al. Reduced glomerular filtration rate in asymptomatic diabetic patients: predictor of increased risk for cardiac events independent of albuminuria. J Am Coll Cardiol. 2004;44(11):2142-8.

20. Stenvinkel P et al. Emerging biomarkers for evaluating cardiovascular risk in the chronic kidney disease patient: how do new pieces fit into the uremic puzzle? Clin J Am Soc Nephrol. 2008;3(2):505-21.

21. Go AS et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;351(13):1296-305.

22. Tonelli M et al. Chronic kidney disease and mortality risk: a systematic review. J Am Soc Nephrol. 2006;17(7):2034-47.

23. Keith DS et al. Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. Arch Intern Med. 2004;164(6):659-63.

24. Antman EM et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction; A report of the American College of Cardiology/

American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of patients with acute myocardial infarction). J Am Coll Cardiol. 2004;44(3):E1-211.

25. Kalantar-Zadeh K et al. Reverse epidemiology of cardiovascular risk factors in maintenance dialysis patients. Kidney Int. 2003;63(3):793-808.

26. Turkmen K et al. Relationship between plasma pentraxin-3, neutrophil-to-lymphocyte ratio, and atherosclerosis in renal transplant patients. Cardiorenal Med. 2012;2(4):298-307.

27. Turkmen K et al. Fetuin-A, inflammation, and coronary artery calcification in hemodialysis patients. Indian J Nephrol. 2011;21(2):90-4.

28. Charytan DM et al. CKD and coronary collateral supply in individuals undergoing coronary angiography after myocardial infarction. Clin J Am Soc Nephrol. 2012;7(7):1079–86.

29. Kasiske BL. Risk factors for accelerated atherosclerosis in renal transplant recipients. Am J Med. 1988;84(6):985-92.

30. Magnus P, Beaglehole R. The real contribution of the major risk factors to the coronary epidemics: time to end the "only-50%" myth. Arch Intern Med. 2001;161(22):2657-60.

31. Sarnak MJ et al. Cardiovascular disease risk factors in chronic renal insufficiency. Clin Nephrol. 2002;57(5):327-35.

32. Lewington S et al. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. Lancet. 2007;370(9602):1829-39.

33. Tsimihodimos V et al. Dyslipidemia in chronic kidney disease: an approach to pathogenesis and treatment. Am J Nephrol. 2008;28(6):958-73.

34. Sechi LA et al. Abnormalities of glucose metabolism in patients with early renal failure. Diabetes. 2002;51(4): 1226-32.

35. Despres JP et al. HDL-cholesterol as a marker of coronary heart disease risk: the Quebec cardiovascular study. Atherosclerosis. 2000;153(2):263-72.

36. Ok E et al. Carbamylated low-density lipoprotein induces death of endothelial cells: a link to atherosclerosis in patients with kidney disease. Kidney Int. 2005;68(1):173-8.

37. Attman PO et al. Lipoprotein metabolism and renal failure. Am J Kidney Dis. 1993;21(6):573-92.

38. KDOQI Clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. http://www.kidney.org/professionals/KDOQI/guidelines_bp/index.htm.

39. Wheeler DC, Becker GJ. Summary of KDIGO guideline. What do we really know about management of blood pressure in patients with chronic kidney disease? Kidney Int. 2013;83:377-83.

40. Chen SC et al. The ratio of observed to predicted left ventricular mass is independently associated with increased cardiovascular events in patients with chronic kidney disease. Hypertens Res. 2012;35:832-8.

41. Prakash S et al. Assessment of hypertension control in chronic kidney disease patients by ambulatory blood pressure monitoring. J Assoc Physicians India. 2005;53:769-74.

42. Andersen MJ et al. Home blood pressure monitoring in CKD. Am J Kidney Dis. 2005;45(6):994-1001.

43. Tucker B et al. Left ventricular hypertrophy and ambulatory blood pressure monitoring in chronic renal failure. Nephrol Dial Transplant. 1997;12(4):724-8.

44. Agarwal R, Andersen MJ. Prognostic importance of ambulatory blood pressure recordings in patients with chronic kidney disease. Kidney Int. 2006;69(7):1175-80.

45. Hansson L, Zanchetti A. The Hypertension Optimal Treatment (HOT) Study--patient characteristics: randomization, risk profiles, and early blood pressure results. Blood Press. 1994;3(5):322-7.

46. Agarwal R, Andersen MJ. Prognostic importance of clinic and home blood pressure recordings in patients with chronic kidney disease. Kidney Int. 2006;69(2):406-11.

47. Sanders CE Jr., Curtis JJ. Role of hypertension in chronic renal allograft dysfunction. Kidney Int Suppl. 1995;52:S43-7.

48. Halloran PF et al. Rethinking chronic allograft nephropathy: the concept of accelerated senescence. J Am Soc Nephrol. 1999;10(1):167-81.

49. London GM et al. Cardiac and arterial interactions in end-stage renal disease. Kidney Int. 1996;50(2):600-8.

50. Takahashi H et al. Autonomic dysfunction in hemodialysis patients with persistent hypotension. Nephron. 1996;72(3):418-23.

51. Jones MA et al. Changes in diurnal blood pressure variation and red cell and plasma volumes in patients with renal failure who develop erythropoietin-induced hypertension. Clin Nephrol. 1995;44(3):193-200.

52. van den Dorpel MA et al. Cyclosporin A impairs the nocturnal blood pressure fall in renal transplant recipients. Hypertension. 1996;28(2):304-7.

53. Lipkin GW et al. Ambulatory blood pressure and left ventricular mass in cyclosporin- and non-cyclosporin-treated renal transplant recipients. J Hypertens. 1993;11(4):439-42.

54. Kayrak M et al. Masked hypertension in renal transplant recipients. Blood Press. 2013. [Epub ahead of print].

55. Agarwal R. Hypertension: KDIGO BP guidelines-more individualized, less prescriptive. Nat Rev Nephrol. 2013;9: 131-3.

56. Wood KJ, Goto R. Mechanisms of rejection: current perspectives. Transplantation. 2012;93(1):1-10.

57. Turkmen K et al. The relationship between oxidative stress, inflammation, and atherosclerosis in renal transplant and end-stage renal disease patients. Ren Fail. 2012;34(10):1229-37.

58. Tamhane UU et al. Association between admission neutrophil to lymphocyte ratio and outcomes in patients with acute coronary syndrome. Am J Cardiol. 2008;102(6):653-7.

59. Nunez J et al. Usefulness of the neutrophil to lymphocyte ratio in predicting long-term mortality in ST segment elevation myocardial infarction. Am J Cardiol. 2008;101(6):747-52.

60. Walsh SR et al. Neutrophil-lymphocyte ratio as a prognostic factor in colorectal cancer. J Surg Oncol. 2005;91(3):181-4.

61. Duffy BK et al. Usefulness of an elevated neutrophil to lymphocyte ratio in predicting long-term mortality after percutaneous coronary intervention. Am J Cardiol. 2006;97(7):993-6.

62. Turkmen K et al. The relationship between neutrophil-to-lymphocyte ratio and inflammation in end-stage renal disease patients. Ren Fail. 2012;34:155-9.

63. Acar G et al. The relation of platelet-lymphocyte ratio and coronary collateral circulation in patients with stable angina pectoris and chronic total occlusion. Clin Appl Thromb Hemost. 2013. [Epub ahead of print].

64. Turkmen K et al. Platelet-to-lymphocyte ratio better predicts inflammation than neutrophil-to-lymphocyte ratio in end-stage renal disease patients. Hemodial Int. 2013;17(3):391-6.

65. Turkmen K. Platelet-to-lymphocyte ratio: one of the novel and valuable platelet indices in hemodialysis patients. Hemodial Int. 2013;17(4):670.

66. Burkly LC et al. TWEAK/Fn14 pathway: an immunological switch for shaping tissue responses. Immunol Rev. 2011;244(1):99-114.

67. Wiley SR, Winkles JA. TWEAK, a member of the TNF superfamily, is a multifunctional cytokine that binds the TweakR/Fn14 receptor. Cytokine Growth Factor Rev. 2003;14(3-4):241-9.

68. Polek TC et al. TWEAK mediates signal transduction and differentiation

of RAW264.7 cells in the absence of Fn14/TweakR. Evidence for a second TWEAK receptor. J Biol Chem. 2003;278(34):32317-23.

69. Justo P et al. Cytokine cooperation in renal tubular cell injury: the role of TWEAK. Kidney Int. 2006;70(10):1750-8.

70. Ortiz A et al. Considering TWEAK as a target for therapy in renal and vascular injury. Cytokine Growth Factor Rev. 2009;20(3):251-8.

71. Yilmaz MI et al. Soluble TWEAK plasma levels as a novel biomarker of endothelial function in patients with chronic kidney disease. Clin J Am Soc Nephrol. 2009;4(11):1716-23.

72. Yilmaz MI et al. Soluble TWEAK and PTX3 in nondialysis CKD patients: impact on endothelial dysfunction and cardiovascular outcomes. Clin J Am Soc Nephrol. 2011;6(4):785-92.

73. Yilmaz MI et al. Predictors of carotid artery intima-media thickness in chronic kidney disease and kidney transplant patients without overt cardiovascular disease. Am J Nephrol. 2010;31(3):214-21.

74. Turkmen K et al. Soluble TWEAK independently predicts atherosclerosis in renal transplant patients. BMC Nephrol. 2013;14:144.

75. Carrero JJ et al. Additive effects of soluble TWEAK and inflammation on mortality in hemodialysis patients. Clin J Am Soc Nephrol. 2009;4(1):110-8.

76. Gungor O et al. The relationships between serum sTWEAK, FGF-23 levels, and carotid atherosclerosis in renal transplant patients. Ren Fail. 2013;35(1):77-81.

77. Moe SM, Chen NX. Mechanisms of vascular calcification in chronic kidney disease. J Am Soc Nephrol. 2008;19(2):213-6.

78. Shioi A et al. Mönckeberg's medial sclerosis and inorganic phosphate in uremia. Am J Kidney Dis. 2001;38(4 Suppl 1):S47-9.

79. Guerin AP et al. Arterial stiffening and vascular calcifications in end-stage renal disease. Nephrol Dial Transplant. 2000;15(7):1014-21.

80. London GM et al. Arterial media calcification in end-stage renal disease: impact on all-cause and cardiovascular mortality. Nephrol Dial Transplant. 2003;18(9):1731-40.

81. Shanahan CM et al. Medial localization of mineralization-regulating proteins in association with Monckeberg's sclerosis: evidence for smooth muscle cell-mediated vascular calcification. Circulation. 1999;100(21):2168-76.

82. Maréchal C et al. Progression of coronary artery calcification and thoracic aorta calcification in kidney transplant recipients. Am J Kidney Dis. 2012;59(2):258-69.

83. Stenvinkel P et al. Are there two types of malnutrition in chronic renal failure? Evidence for relationships between malnutrition, inflammation and atherosclerosis (MIA syndrome). Nephrol Dial Transplant. 2000;15(7):953-60.

84. Wang AY et al. Associations of serum fetuin-A with malnutrition, inflammation, atherosclerosis and valvular calcification syndrome and outcome in peritoneal dialysis patients. Nephrol Dial Transplant. 2005;20(8):1676-85.

85. Stenvinkel P et al. Malnutrition, inflammation, and atherosclerosis in peritoneal dialysis patients. Perit Dial Int. 2001;21 Suppl 3:S157-62.

86. Tonbul HZ et al. Malnutrition-inflammation-atherosclerosis (MIA) syndrome components in hemodialysis and peritoneal dialysis patients. Ren Fail. 2006;28(4):287-94.

87. Haydar AA et al. Coronary artery calcification is related to coronary atherosclerosis in chronic renal disease patients: a study comparing EBCT-generated coronary artery calcium scores and coronary angiography. Nephrol Dial Transplant. 2004;19(9):2307-12.

88. Raggi P et al. Cardiac calcification in adult hemodialysis patients. A link between end-stage renal disease and cardiovascular disease? J Am Coll Cardiol. 2002;39(4):695-701.

89. Caliskan Y et al. Coronary artery calcification and coronary flow velocity in haemodialysis patients. Nephrol Dial Transplant. 2010;25(8):2685-90.

90. Baber U et al. Coronary plaque composition, morphology, and outcomes in patients with and without chronic kidney disease presenting with acute coronary syndromes. JACC Cardiovasc Imaging. 2012;5(3 Suppl):S53-61.

91. Kawai H et al. Coronary plaque characteristics in patients with mild chronic kidney disease. Circ J. 2012;76:1436-41.

92. Acharji S et al. Prognostic significance of elevated baseline troponin in patients with acute coronary syndromes and chronic kidney disease treated with different antithrombotic regimens: a substudy from the ACUITY Trial. Circ Cardiovasc Interv. 2012;5(2):157-65.

93. Shroff GR et al. Renal failure and acute myocardial infarction: clinical characteristics in patients with advanced chronic kidney disease, on dialysis, and without chronic kidney disease. A collaborative project of the United States Renal Data System/National Institutes of Health and the National Registry of Myocardial Infarction. Am Heart J. 2012;163(3):399-406.

94. Kasiske BL et al. Acute myocardial infarction and kidney transplantation. J Am Soc Nephrol. 2006;17(3):900-7.

95. Wolf M. FGF23: fashion or physiology? Clin J Am Soc Nephrol. 2010;5(10):1727-9.

96. Baia LC et al. Fibroblast growth factor 23 and cardiovascular mortality after kidney transplantation. Clin J Am Soc Nephrol. 2013;8(11):1968-78.