Cardiorenal Intersection: Crossroads to the Future

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The pandemic of obesity is driving secondary epidemics of type 2 diabetes, dysmetabolic syndrome, and hypertension. This results in increasing numbers of patients with renal disease and coronary atherosclerosis. Chronic kidney disease accelerates the course of coronary artery disease, independent from conventional cardiac risk factors. In addition, chronic kidney disease is associated with left ventricular hypertrophy and myocardial fibrosis, aortic and mitral valvular disease, and both atrial and ventricular arrhythmias. As a result, for patients on hemodialysis, sudden unexplained death is common and often attributed to heart disease. This article reviews the evidence for accelerated atherosclerotic heart disease in the presence of renal disease and highlights new diagnostic and therapeutic targets at these crossroads.

Accelerated atherogenesis in Cronic Kidney Disease

As adult populations age in the coming decades, the rates of virtually all chronic diseases are expected to rise. Currently, tens of millions of persons worldwide have combined cardiovascular disease (CVD) and chronic kidney disease (CKD)[1]. In the United States alone, over 300,000 individuals are on renal replacement therapy (RRT), which confers a 5 to 40-fold increased risk of fatal cardiovascular events[2-5]. CKD is commonly defined as an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2, or the presence of an elevated urinary albumin to creatinine ratio > 30 mg/g on a spot urine sample. A reduction in eGFR below that expected for age is a surrogate for reduced renal parenchymal mass and a partial loss of normal regulatory functions such regulation of blood pressure, erythropoiesis, and other vasculoprotective processes resulting in higher adjusted rates of CVD events in populations (Fig. 1). A new measure of renal filtration function is cystatin-C, a cysteine protease inhibitor produced by all nucleated cells which is freely filtered and completely reabsorbed at the level of the proximal tubule. This blood test has recently been cleared by the US FDA as a new measure of renal filtration function in addition to serum creatinine and blood urea nitrogen[6]. Microalbuminuria is a reflection of endothelial and vascular injury at the level of the glomeruli and is associated with all vascular risk factors that relate to vessel damage (Fig. 2). Thus these two measures reflect different aspects of

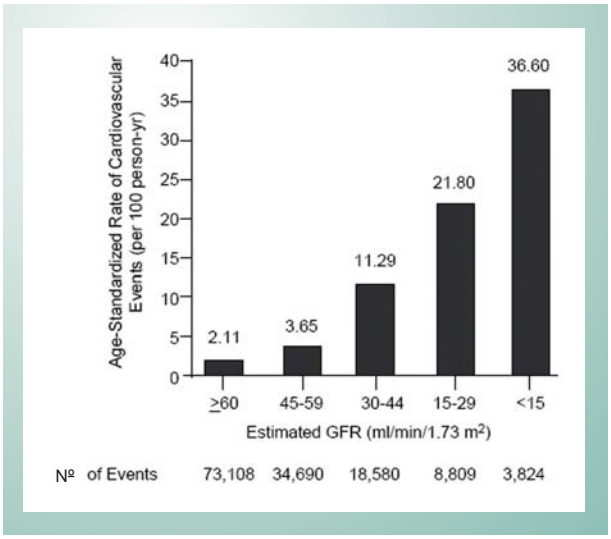

Fig. 1 - *Adjusted risks of cardiovascular events stratefied by level of eGFR in patients from a vertically integrated health system followed over ~5 years. All variables known to be associated with either the eGFR or the outcomes were included in the final models (sociodemographic status, prior CVD, prior hospitalizations, DM, HTN, dyslipidemia, lung or liver disease, cancer, albumin ≤ 3.5 g/dl, dementia, proteinuria, and the initiation of dialysis during followup). Reproduced with permission from reference[58].*

cardiorenal risk[7]. Although conventional risk factors such as hypertension, diabetes mellitus (DM) and dyslipidemia are commonly associated with CKD and its attendant long-term CVD morbidity, these risk factors alone do not fully explain the prevalence of CVD in this population. Novel risk factors such as homocysteinemia (Hcy), elevated lipoprotein (a) [Lp(a)], oxidative stress, endothelial dysfunction, anemia, diminished transforming growth factor-ß1 (TGF-ß1), chronic inflammation and vascular calcification are increasingly linked to accelerated rates of atherogenesis in the setting of CKD.

Increased conventional CVD risk factors in CKD

Lifestyle and diet

Given the clustering of risk factors associated with obesity and type 2 DM, excess adiposity due to a sedentary lifestyle

Key words
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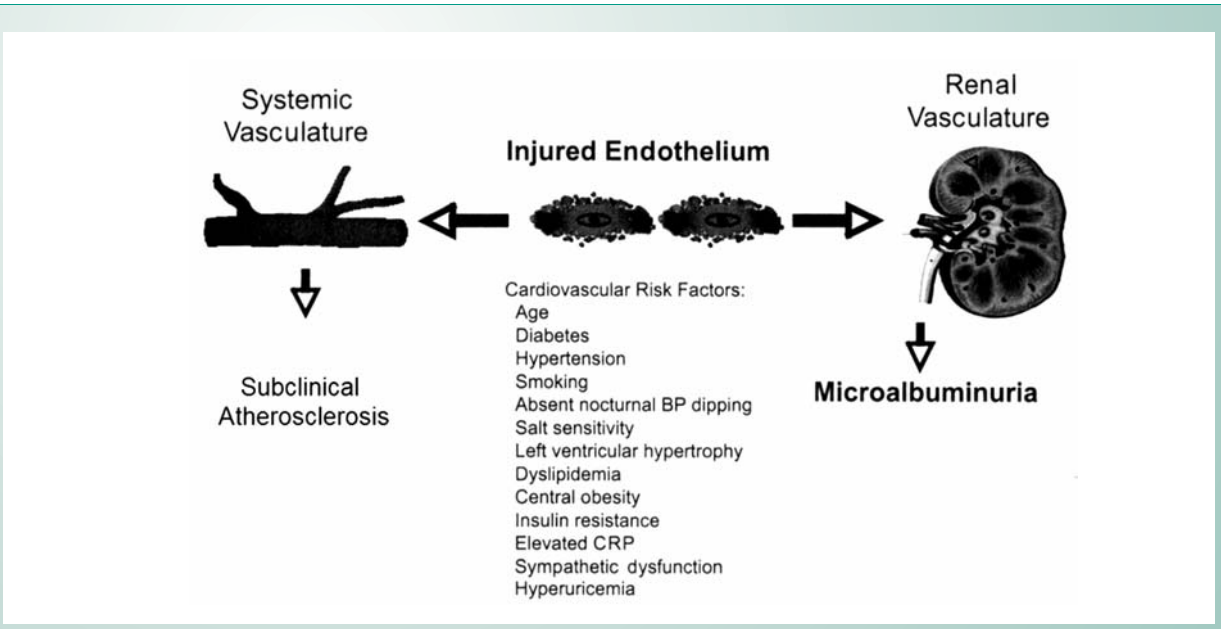

Fig. 2 - *Relationship to observed microalbuminuria and vascular disease.*

and poor dietary habits, including an excessive intake of sugars, simple carbohydrates, and saturated fats, is common among patients with, at early CKD. It is now widely recognized that the CKD that develops in the setting of DM begins to become manifest at the dysmetabolic syndrome stage of disease. Excess adiposity and its related increased levels of inflammatory factors have been implicated in an "obesity-related glomerulopathy"[8]. This form of glomerulopathy is recognized by the presence of microalbuminuria with preserved renal filtration function and is reversible with significant weight loss. Weight reduction has also been shown to markedly improve blood glucose control and, in some cases, result in the apparent resolution of DM[9]. Moreover, exercise training programs can improve the conventional cardiac risk profile of renal transplant recipients[10]. Although there have been no prospective, comparative studies of diet and lifestyle changes on CVD outcomes in patients with CKD, normalization of body weight and fat stores, reduction in sodium intake, and regular aerobic exercise would be expected to have a salutary impact on this escalating patient population (Tab. 1). Given the expected higher rates of novel risk factors including endothelial dysfunction, oxidative stress and inflammation, intensive lifestyle modification, including dietary changes and regular aerobic exercise, may reduce the incidence of CVD in this population[11]. In addition, any therapeutic agent that causes even a mild reduction in adiposity can be expected to have significant favorable effects on systemic inflammatory factors, insulin sensitivity, blood pressure, and lipids. One such therapy is rimonabant, an endocanniboid receptor antagonist which has been demonstrated to induce a modest weight loss in the overweight and mildly obese populations tested thus far. This drug works by reducing the hunger stimulus of endogenous canniboid-like substances in the central nervous system. Unfortunately, when the drug is stopped, the weight is predictably regained[12].

Hypertension

As renal function worsens, the blood pressure predictably rises and becomes more difficult to control. The renin-angiotensin system (RAS) and sympathetic nervous system are aberrantly activated, resulting in increased afterload, left ventricular enlargement, greater myocardial oxygen consumption, and augmented sheer stress at the endothelial level in patients with CKD[13]. Opportunities for modulation of the RAS within the vascular tree occur at several points (Fig. 3). Additionally, many CKD patients with hypertension develop left ventricular hypertrophy (LVH), resulting in an increased myocardial mass to endothelial surface area, and an unfavorable myocardial oxygen supply and demand relationship. Hyperactivation of the RAS leads to expression of oxidized low-density lipoprotein receptors and acceleration of atherosclerosis (Fig 3). As eGFR declines, systemic blood pressure rises causing greater sheer stress, increased risk of plaque rupture, and episodic coronary occlusion. Consequently, blood pressure control to a target systolic blood pressure < 130 mmHg (ideally < 120 mmHg) is currently recommended (Tab. 1). Since both the RAS and the sympathetic nervous systems are hyperactivated in CKD, the most promising therapeutic agent for future use beyond currently available angiotensin converting enzyme inhibitors, beta-adrenergic receptors blockers, and angiotensin II receptor antagonists, is the renin inhibitor aliskiren[14]. Since the sympathetic nervous system triggers the release of renin from the juxtaglomerular cells in the kidney, binding renin and impeding its conversion of angiotensinogen to angiotensin I could have a significant favorable impact in patients with CKD.

Diabetes Mellitus

Diabetes and hypertension often develop at the same time in patient who will later develop CKD. Over 40% of

Preventive Measure	Rationale
Generally Accepted	
Weight loss/weight maintenance at BMI < 25 kg/m^2	Resolution of the dysmetabolic syndrome Prevention of/improvement in DM
Aerobic exercise/strength training 30 min/day most days of the week	Primary/secondary prevention of MI, stroke, and CVD death Improvement in other risk factors in CKD patients
Low sodium intake	Reduce blood pressure Make blood pressure more responsive to medications
Avoidance of NSAIDS	Reduced risk of superimposed NSAID nephropathy Reduced risk of fluid retention and heart failure
Aspirin 81 mg p.o. q.d.	Primary/secondary prevention of MI and stroke
Lipid control (diet, statin, fibrates, niacin, others) -LDL-C < 70 mg/dl -TG < 150 mg/dl -HDL-C > 50 mg/dl	Attenuate vascular calcification Primary/secondary prevention of MI, stroke, and CVD death Possible reduction in progression of CKD
Blood pressure control to optimal target of SBP < 120 mmHg -RAS blocking agents -add-on therapy	Primary/secondary prevention of MI, stroke, heart failure, and CVD death Reduce/normalize microalbuminuria Slow the progression to ESKD and death
Blood glucose control in DM to target glycohemoglobin < 6 mg/dl	Reduction in risk of MI, stroke, and CVD death Reduction in worsened nephropathy/retinopathy
Experimental - Limited Supportive Evidence	
Reduce/normalize Lp (a) levels < 30 mg/dl -Niacin -Lipid apheresis	Possible primary/secondary prevention of MI, stroke, and CVD death
NAC 600 mg p.o. bid in ESKD	Reduce composite CVD events
NAC 1,200 mg IV pre- and 1,200 mg p.o. bid post-contrast exposure	Reduce CIN events and associated mortality in acute infarct coronary intervention
Ascorbic acid 3 g p.o. pre- and 2 g p.o. bid post-contrast exposure	Reduce CIN events
Evidence for No Benefit or Harm	
Anemia correction in CKD to Hb > 13.0 g/dl	Increased rates of CVD events, primarily HF hospitalizations

BMI = body mass index, NSAIDS = non-steroidal anti-inflammatory drugs, LDL-C = low-density lipoprotein cholesterol, TG = triglycerides, HDL-C = high density lipoprotein cholesterol, SBP = systolic blood pressure, RAS = renin angiotensin system, MI = myocardial infarction, CVD = cardiovascular disease, CKD = chronic kidney disease, ESKD = end-stage kidney disease, NAC=N-acetylcysteine.

Table 1 - Primary and secondary CVD prevention strategies for patients with CKD

end-stage kidney disease (ESKD) is secondary to diabetic nephrosclerosis, and 48 to 57% of patients with DM have overt diabetic nephropathy[1]. Patients with DM have significantly elevated levels of serum insulin, a potent growth factor for atherosclerosis, in addition to a dyslipidemic state. The epidemic of DM so measurably impacts CVD that the most recent National Cholesterol Education Program (NCEP) adult treatment panel guidelines (ATP-III) listed DM as a CVD equivalent, and recommend treating afflicted patients accordingly to even lower target levels of low-density lipoprotein cholesterol (LDL-C)[15]. In those with excess adiposity and type 2 DM, weight reduction is the intervention of choice to improve or resolve the diabetic condition[9]. Optimal glycemic control (glycohemoglobin < 6 %) has been shown to reduce microvascular events (retinopathy) and, along with blood pressure lowering, decrease the incidence of macrovascular events (myocardial infarction, stroke, and CVD death) in patients with type 1 or type 2 DM.

Currently available agents in the United States which have consistently demonstrated a mild (2-4 kg) drop in weight as a side-effect include alpha-glucosidase inhibitors, metformin, and exenatide[16]. Forms of insulin that appear to be weight neutral are the very long acting glargine insulin and detemir insulin. Importantly, all shorter acting forms of insulin and thiazolidinediones cause increases in adiposity and despite better glucose control and possible other favorable CVD effects, the weight gain is a strong deterrent to their use in the obese patient[17].

Dyslipidemias

The uremic environment affects multiple areas of lipoprotein metabolism including an impairment of lipoprotein lipase. Dyslipidemias occur in up to 67% of CKD patients[18]. This patient population often demonstrates diminished levels of cardioprotective high-density lipoprotein cholesterol (HDL-C), and atherogenic elevations in triglycerides and LDL-C. In particular, CKD patients have heightened concentrations of apolipoproteins AIV and B48. Furthermore, uremic stress results in increased levels of oxidized LDL-C, a highly reactive and atherogenic species. Thus, it appears that hyperactivation of the RAS, elevated insulin levels, and the dyslipidemia of CKD work in concert to advance atherosclerosis at faster rates than in those with preserved renal function[19]. It is not surprising that the kidney as the most vascular organ is affected by the atherosclerotic process beyond the large renal artery and its major subbranches. Thus, diffuse endothelial dysfunction and atherosclerosis are believed to be part of the common pathophysiology in diabetic and non-diabetic CKD, particularly in older adults. A meta-analysis by Fried and co-workers published in 2001 in a total of 362 patients with CKD in small trials suggested that treatment of dyslipidemia was associated with a relative 1.9 ml/min/year benefit in sparing of eGFR compared to controls[20]. A recently published analysis from the Rosuvastatin Clinical Development Program analyzed the results pooled from 13 studies involving 3,956 patients treated with rosuvastatin or placebo. In those with an eGFR < 60 ml/min, there was a $+2.8$ ml/min improvement over 22 months[21]. The Study of Heart and Renal Protection (SHARP) is an ongoing, prospective, open-label randomized trial, n $= 9{,}000$, testing the treatment effect of lowering LDL-C in CKD. The main aim of this study is to test whether reducing blood cholesterol with a combination tablet, containing both simvastatin and ezetimibe, can prevent myocardial infarction, cardiac death, stroke, and revascularization in patients with CKD ($\sim$6,000 pre-dialysis and $\sim$3,000 on dialysis). Additionally, the trial will test the effect on LDL-C of combining ezetimibe with simvastatin, as compared with simvastatin alone. The trial will also be able to study a number of other potential effects of lowering cholesterol, including whether it can delay the need for dialysis in CKD. Finally, since a low HDL-C is the most prominent lipid abnormality in CKD, agents that significantly raise HDL-C such as cholesterol ester transferase protein inhibitors are particularly promising[22]. Large trials are underway in the general population testing the concept of raising HDL-C to lower rates of incident CVD events. Current guidelines support the lipid targets given in Table 1 and depicted in Figure 4[15].

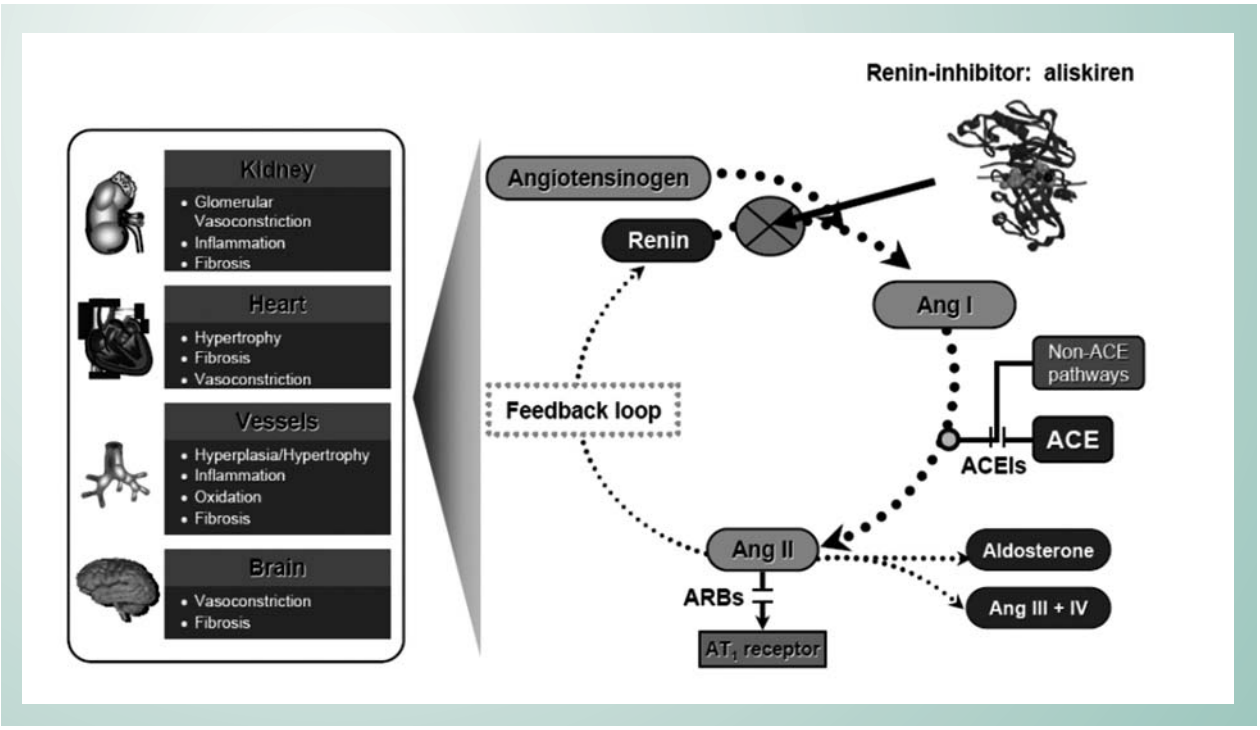

Fig. 3 - *Angiotensinogen is secreted by the liver and is cleaved by renin, which is secreted into the lumen of renal afferent arterioles by juxtaglomerular cells. Angiotensin I is then converted to angiotensin II by angiotensin-converting enzyme primarily in endothelial cells. In the zona glomerulosa of the adrenal cortex, angiotensin II stimulates the production of aldosterone. Aliskiren binds renin making it unable to cleave angiotensinogen. Renin-angiotensin-aldosterone system (RAAS); angiotensin-converting enzyme inhibitor (ACEI); angiotensin receptor blockers (ARB); angiotensin (Ang); angiotensin-converting enzyme (ACE); type 1 angiotensin II receptor (AT1).*

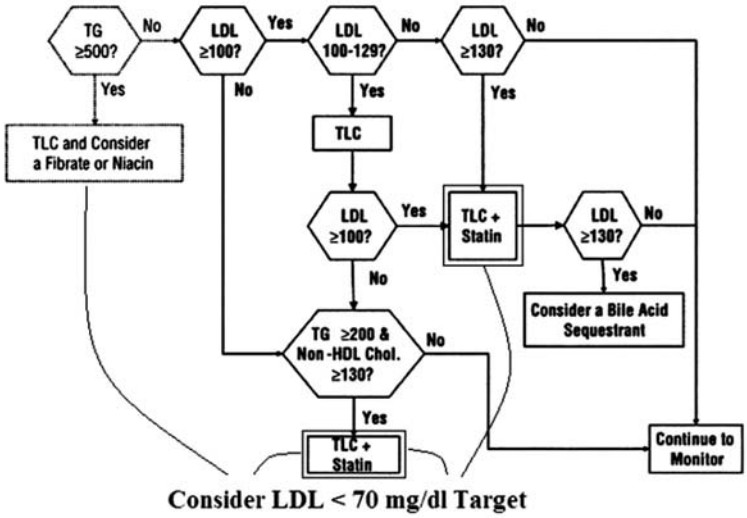

Fig. 4 - *Suggested treatment algorithm for the management of dyslipidemia by K/DOQI. TG = triglycerides, LDL = low-density lipoprotein cholesterol, non HDL = non-high density lipoprotein cholesterol (total cholesterol – HDL), TLC = therapeutic lifestyle changes.*

Novel coronary disease risk factors

Homocysteinemia

Homocysteine (Hcy), a product of methionine metabolism, is increased 2 to 4-fold in patients with CKD, as renal tubular excretion normally accounts for 70% of Hcy clearance[w]. When the eGFR drops below 60 ml/min/1.73 m^2, Hcy is predictably elevated. Furthermore, mean Hcy levels are increased 14 to 20% in ESKD patients with CVD compared to those without[23]. Patients with elevated Hcy levels have a 3 to 4-fold increased CVD event rate and a 10.9-fold increased cerebrovascular event rate[24]. Hcy levels inversely correlate with red blood cell folate levels. Accordingly, supratherapeutic doses of folic acid (5 to 20 mg daily) and vitamin-B12, both components of Hcy metabolism, may decrease Hcy levels by 20 to 55% in ESKD patients[25]. Recent trials in the general population indicate that lowering homocysteine with the vitamins indicated above does not lower rates of CVD events[26]. Emerging data in patients with CKD also confirm this concept[27]. So despite the epidemiologic and pathophysiologic data on homocysteine and CVD, it appears that this protein will not be a clinical target in the future.

Lipoprotein (a)

Lipoprotein (a) [Lp(a)] levels are increased 43% in patients on RRT as compared with the general population[28]. In addition, CKD patients have higher levels of the low-molecular weight isoforms, which have even more pronounced atherogenic characteristics. Lp(a) is elevated in 64% of RRT patients with CVD in contrast to 3.8% of those without[29]. The putative atherogenic mechanism of Lp(a) includes macrophage foam cell production, inhibition of fibrinolysis, and adverse effects on endothelial-dependent vascular reactivity. Preliminary studies demonstrate that Lp(a) levels may be reduced with niceritrol (a niacin prodrug), plasma apheresis and renal transplantation[30]. In addition, pyrazole derivatives as partial agonists for the nicotinic acid receptor may be future therapeutic targets for decreasing Lp(a) levels[31].

Oxidative stress

Oxidative stress has been implicated in two basic cardiovascular areas: impaired endothelial function and acceleration of lipid accumulation in atherosclerotic plaque[32]. Patients with CKD and ESKD experience significant oxidative stress manifested by abundant glycosylation products and oxidized proteins such as LDL-C (Fig. 5). Oxidative stress has profound atherogenic effects as reactive oxygen species combine with nitric oxide resulting in endothelial dysfunction. Preliminary studies in ESKD patients have demonstrated that N-acetylcysteine decreases the levels of oxidized LDL-C by 76%, and the composite end-points of non-fatal myocardial infarction, cardiovascular death, revascularization, and ischemic stroke by 40%. While antioxidants have not reduced CVD events in the general population, clinical trials of antioxidant use in ESKD patients reported reductions in morbidity and mortality[33]. The most promising use of antioxidants is in the prevention of acute renal failure due to contrast-induced nephropathy. In this application, clinical trials have demonstrated that pre- and post-contrast exposure treatment with N-acetylcysteine or ascorbic acid reduces the rate of kidney injury in those patients at risk[34,35].

Endothelial dysfunction

The vascular endothelium is the body's largest organ, and local paracrine control of endothelial function appears to be critical in vascular health and disease. Patients with CKD have increased levels of asymmetric dimethyl arginine, a nitric oxide

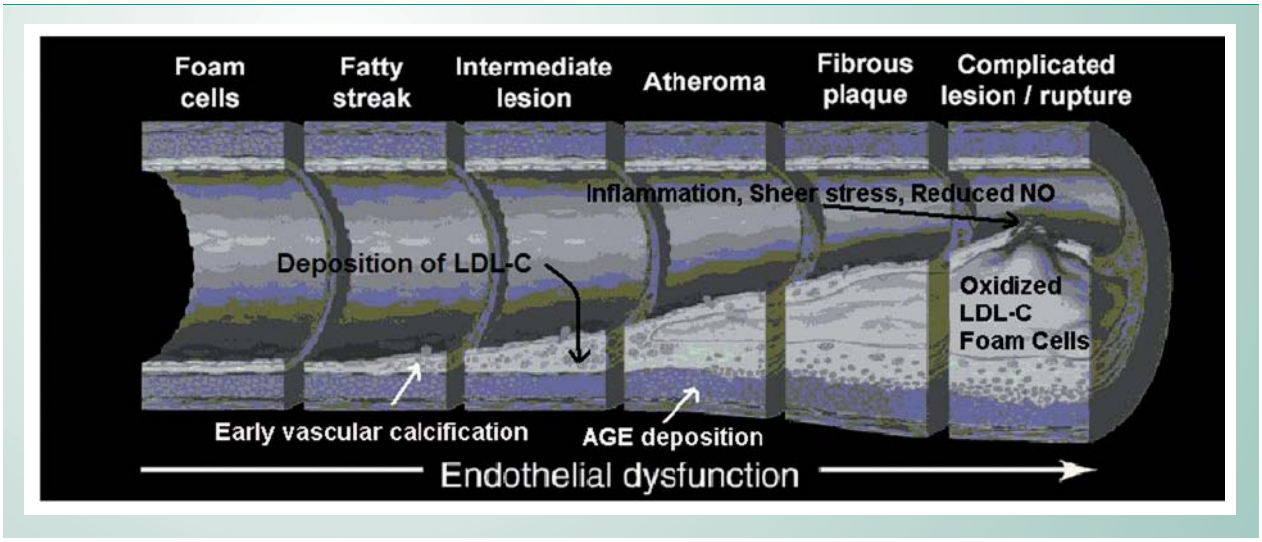

Fig. 5 - *The processes related to the acceleration of coronary disease and plaque rupture in patients with renal disease. NO=nitric oxide, LDL-C=low density lipoprotein cholesterol, AGE=advanced glycation end products.*

synthase inhibitor, and correspondingly diminished levels of nitric oxide, a potent coronary vasodilator and an important local factor in endothelial function[36]. Other aberrancies of CKD include elevated endothelin production and reduced thrombomodulin expression. The end-result is impairment of coronary flow reserve and the myocardial microcirculation. Hyperactivation of the RAS further negates the actions of nitric oxide, inhibiting endothelium-dependent vasodilation, and hastening the inexorable progression of coronary disease (Fig 5). Of note, in the process of anemia correction with erythrocyte stimulating proteins (erythropoietin, darbepoetin) with supplemental iron, levels of asymmetric dimethyl arginine further elevated and there is an even greater impairment of nitric oxide[37]. Results of clinical trials of anemia correction in CKD indicate that near normalization of the hemoglobin level has resulted in higher rates of CVD events[38,39]. Thus it appears that anemia correction, because of its adverse effects on endothelial function, anemia or hemoglobin will not be a CVD therapeutic target in CKD.

Transforming growth factor

Transforming growth factor beta-1 (TGF-ß1) has pleiotropic effects which include inhibiting smooth muscle cell proliferation and monocyte-macrophage migration as well as providing a direct protective effect on the vascular endothelium. In ESKD patients, serum levels of TGF-ß1 are reduced as compared with the general population, and may result in accelerated atherosclerosis. TGF-ß1 levels have been shown to be reduced in CKD patients with CVD or peripheral arterial disease. Furthermore, patients with triple vessel coronary artery disease have even greater reductions of serum TGF-ß1. For every 1 ng/ml decrease in TGF-ß1 there appears to be a corresponding increase (~9%) in the CVD event rate[40]. In addition, decreases in TGF-ß1 have been linked to bone disease[41]. However, studies of atherosclerosis indicate that TGF-ß1 regulation is altered by cytokines and thus is implicated in the pathogenesis of vascular disease[42]. Until this cell signaling protein is better understood, these data suggest that TGF-ß1 is not likely to be a therapeutic target in the near future.

Chronic inflammation

Excess adiposity, particularly intra-abdominal fat results in increased serum levels of positive acute phase reactants such as C-reactive protein (CRP), fibrinogen, ferritin, interleukin-6 (IL-6) and Lp(a)[43]. In addition, there is a corresponding decrease in negative acute phase reactants such as albumin, prealbumin, cholesterol, and apolipoprotein A1 and B. Secreted by adipocytes, IL-6 potently induces hepatic synthesis of CRP, which binds to the Fc-receptor of the immunoglobulin protein, and subsequently activates the complement cascade. Chronic inflammation commonly occurs in ESKD as a result of intercurrent illnesses such as glomerulonephritis and infection, as well as RRT specific factors, including exposure to water-born endotoxins and bioincompatible dialysis membranes[44]. An elevated serum CRP level is one of the most powerful predictors of mortality in patients on RRT and portends a 4.6-fold increased risk of CVD death[45]. In addition to abnormal CRP levels, ESKD patients are 10.6-fold more likely to have elevated fibrinogen levels as part of the acute phase response, which may result in increased plasma viscosity, endothelial injury and thrombosis. As mentioned above, superimposed obesity, through the production of IL-6 stimulates hepatic production of CRP and further worsens the systemic inflammatory state. Plasma apheresis has been shown to effectively reduce the acute phase reactant fibrinogen in ESKD patients. While inflammatory factors may be slightly elevated in those with normal renal function, they are disproportionately high in CKD and should be treated with aspirin and statin therapy[46]. Importantly, the single most potent method for reducing CRP is reducing abdominal adiposity through weight loss[47].

Coronary calcification

Patients on RRT have coronary calcification scores far exceeding those of the general population, including those

found in younger patients. Coronary calcification as measured by computed tomography is present in 88% of ESKD patients between the ages of 20 and 30 years in contrast to 5% of age-matched controls[48]. In addition, serum calcium and phosphate levels as well and serum lipids interact to significantly impact vascular calcification[49]. ESKD patients on non-calcium based phosphate binders are less likely to have vascular calcification within the coronary arteries (0 versus 37%, p=0.03) and thoracic aorta (0 versus 75%, p=0.01) after a 52-week follow-up period as compared with ESKD patients on calcium-based phosphate binders[50]. There was a large reduction in the final LDL-C levels with sevelamer compared to calcium-based binders, 65 vs 103 mg/dl, respectively, p < 0.0001. This is consistent with the known bile-acid sequestrant properties of sevelamer. Accordingly, there was attenuation of progression of CAC with sevelamer with no differences in CPP or PTH, suggesting the change in CAC was more related to LDL-C reduction. While vascular calcification cannot be reversed with current therapies, it appears that LDL-C reduction with sevelamer and statins attenuates progression in humans. In a study of 66 subjects who were followed during a periods without statin treatment and then during treatment with cerivastatin 0.3 mg p.o. qd, the overall median annualized relative change was significantly higher in the untreated interval compared with the treated interval (25% vs 8.8%, P< 0.0001)[51]. The annualized relative change of the CAC score in 32 patients who achieved an LDL-C level of < 100 mg/dL decreased from 27% to -3.4% (P< 0.0001). Callister and colleagues reported on 149 patients with CAD, 105 of whom were taking statins, undergoing baseline and then follow-up electron beam computed tomography studies at 12-15 months[52].

The concept of LDL-C reduction and stabilization of coronary atherosclerosis has been extended to the Dialysis Clinical Outcomes Revisited (DCOR) trial, the largest outcomes study ever conducted in the hemodialysis population. The three-year trial involving more than 2,100 patients compared the difference in mortality and morbidity outcomes for patients receiving sevelamer hydrochloride versus those using calcium-based phosphate binders. Despite the LDL-C reduction with sevelamer, there was no reduction in mortality between the treatment groups (9% relative risk reduction with sevelamer, p = 0.30)[53]. Thus stabilization of the progression of CAC may be a benefit of LDL-C reduction, in ESKD it does not appear to be related to changes in mortality in this group. The latest results came from the "4D Trial" (Deutsche Diabetes Dialyse Studie) where 1,255 type 2 DM patients with new ESKD were randomized to atorvastatin 20 mg p.o. qd or placebo for a median of 4 years[54]. The statin was effective in reducing the median serum LDL-C by 42% throughout the study period. However, the primary endpoint—defined as the composite of cardiac death, nonfatal MI, and fatal or nonfatal stroke—was only reduced by 8% with atorvastatin, p = 0.37. The 4D investigators concluded that the negative results might have been due to the advanced cardiovascular diseases in the chronic HD patients, and because statin therapy was initiated too late. It appears from DCOR and 4D, that LDL-C reduction in ESKD may not impact on cardiovascular events or mortality due to the advanced disease present by the time ESKD develops, competing cardiovascular mechanisms for terminal events in ESKD (nonischemic arrhythmias, bradycardia, etc), and the high rates competing noncardiovascular sources of mortality (sepsis, venous thromboembolism, etc).

Platelet aggregability

Uremia causes decreases in platelet aggregation[55]. In ESKD patients, exposure to heparin, bioincompatible dialysis membranes and arteriovenous shunts may result in superimposed increased platelet aggregation. Similar effects on platelet aggregation have been shown in chronic ambulatory peritoneal dialysis patients and CKD patients with hypertriglyceridemia. Nonetheless, many CKD patients at risk for CVD do not receive antiplatelet therapy due to concerns over platelet dysfunction and the potential for bleeding complications. The combination of excess thrombin generation and decreased platelet aggegability make the patient with CKD at risk, simultaneously, for thrombotic events and hemorrhage. In general, low-dose daily aspirin is recommended for those with CKD, since it is considered a CVD-risk equivalent state. Emerging sources of data suggest in the CKD patient with acute coronary syndrome, that bivalirudin may be the antithrombotic with the best benefit to bleeding risk ratio[56].

Cardioprotective therapies

Studies have consistently shown that CKD patients presenting with acute myocardial infarction are less likely to receive standard therapies. For example, ESKD patients are less likely to receive cardioprotective medications such as aspirin, heparin, ß-blockers and angiotensin converting enzyme inhibitors, and are 51% less likely to receive reperfusion therapy for acute myocardial infarction as compared with patients with normal renal function[57]. In general, patients with CKD have a greater relative risk reduction with aspirin, beta-blockers, angiotensin-converting enzyme inhibitors (ACEI), glycoprotein IIb/IIIa inhibitors, and lipid lowering therapy as compared with the general population after an acute coronary event. Efforts should be made to improve the quality of medical care to coronary patients with CKD and future randomized trials of contemporary therapies should target this at-risk population[58].

Conclusion

The crossroads between heart and kidney disease have led investigators to consider new approaches to atherosclerosis. Understanding that patients with renal disease have a high prevalence of CVD and its associated sequelae, which is only partially explained by conventional CVD risk factors such as hypertension, DM, and dyslipidemia. Novel CVD risk factors in CKD patients appear to play a critical role in the acceleration of the atherosclerotic process. Understanding the mechanisms of these novel factors may lead to specific therapies both for the CKD and the general population.

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