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Mechanisms for increased cardiovascular disease in chronic kidney dysfunction

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Abstract

Purpose of review—Patients with chronic kidney disease (CKD) have the highest risk for atherosclerotic cardiovascular disease (CVD). Current interventions have been insufficiently effective in lessening excess incidence and mortality from CVD in CKD patients versus other high-risk groups. This review focuses on traditional and CKD-related risks as well as key mechanisms of macrophage foam cell formation that underlie the excess CVD in the setting of CKD.

Recent findings—Hyperlipidemia, particularly increased low density lipoprotein (LDL) cholesterol, is the key factor in atherogenesis in the general population, but has not been found to be the overriding risk for greater CVD in CKD, especially as renal damage progresses. Although higher incidence of CVD in CKD is not due to higher serum lipids *per se*, CKD is associated with abnormal lipid metabolism that is proatherogenic. CKD-related risks, including inflammation and disturbances in mineral metabolism, have been implicated. In addition, perturbations of the macrophage, a cell that is central in atherogenesis, may be important.

Summary—The mechanisms underlying the heightened risk for CVD in CKD have been the focus of intense study and may relate to the combined effects of traditional and CKD-specific risks involving inflammation and lipid metabolism, especially perturbation of macrophage cholesterol homeostasis.

Keywords

ABCA1; atherosclerosis; cholesterol; CKD; macrophage

Introduction

Accelerated atherosclerosis and increased cardiovascular events have been extensively documented in patients with end stage chronic kidney disease (CKD) [1–3]. However, accumulating evidence underscores the increased risk for cardiovascular events that prevails at every stage of CKD [4–6]. A graded association between glomerular filtration rate (GFR) and cardiovascular deaths begins with subtle decrease in GFR ($<60\text{--}80\text{ml/min/1.73m}^2$) which imparts an independent risk of death, acute cardiovascular events, hospitalization, and more cardiovascular complications following a myocardial infarct [4,5]. Even microalbuminuria, in the absence of apparent decrease in renal function or diabetes, predicts more cardiovascular disease (CVD) and death [6]. The impact of CVD in CKD is illustrated by reports on the natural history of patients with early CKD, which find that the risk of premature CVD death is much

higher than the risk of progressing to dialysis/transplantation [7,8]. Such observations are significant not only because of the high incidence and prevalence of end stage CKD, but because the number of patients with early CKD far exceeds those with end stage CKD and this trend is continuing to rise [9]. The concern is further heightened by the recent findings of low prevalence of awareness of kidney disease among adults in the United States with or without coronary artery disease [10•]. These findings have prompted new recommendations that all patients with cardiovascular disease be systematically screened for CKD [11] and that the presence of even subtle renal dysfunction should prompt intense efforts to decrease cardiovascular risks.

Risk factors

There is little doubt that renal dysfunction is associated with excessive CVD, however, it remains uncertain how renal dysfunction/failure imparts the heightened risk. Hyperlipidemia, diabetes mellitus, hypertension, obesity, smoking, advanced age and male gender are all well known risk factors for developing cardiovascular disease in the general population. Although CKD *per se* appears to predispose to CVD, it is also possible that CKD simply identifies individuals with more severe, long-standing, or poorly controlled risks, that is, diabetes or hypertension. This possible limitation notwithstanding, recognition of risk factors is important, as some of these are modifiable and implementation of risk-factor-reducing programs and therapeutic interventions has successfully lessened overall morbidity and mortality in the general population. Thus, from 1980 through 2000, death rate from coronary artery disease fell by more than 40%, with half of the decline attributable to reduction in major risk factors and the other half to therapeutic interventions [12•]. By contrast, no such trend has occurred in CKD and end stage renal disease (ESRD) patients, whose mortality has been estimated to be between 5 and 500 times higher than age-matched normal populations (Fig. 1) [13,14].

The traditional, that is, Framingham, risk factors of hypertension, diabetes mellitus, older age that predict cardiovascular disease in the general population, are increased in CKD and have been shown to predict cardiovascular mortality in the CKD patients [15–18]. However, the impact of an individual risk is not uniform across the spectrum of CKD and depends on the patient population, the degree of renal dysfunction and the etiology of kidney disease [17,19–22]. In addition, some studies find that specific risks in the setting of CKD deviate from the effects observed in the general population. For example, in patients with ESRD, elevated serum cholesterol, higher blood pressure and increased BMI are not consistently associated with acute cardiac events or all-cause mortality [20,21]. Indeed, ‘reverse epidemiology’, that is, higher cholesterol, blood pressure and BMI have been reported to predict a better outcome in these individuals (see below) [22]. Further, statistical adjustments for traditional risks have not been able to fully explain the predisposition for CVD in CKD, raising the possibility of nontraditional risks that may be specific to CKD.

The cardiovascular risk factors that have been postulated to be especially relevant to CKD include malnutrition/low serum albumin, anemia, hyperhomocysteinemia, elevated fibrinogen, dysregulation of calcium/phosphorus, oxidative stress and inflammatory factors [19,23•,24–26]. Oxidative stress and inflammation have recently gained considerable support as factors relevant in CVD in the setting of CKD. For example, the highest tertiles of high sensitivity C-reactive proteins and IL-6 were each associated with doubling in the risk for sudden cardiac death compared with the lowest tertiles [21,23•,27,28]. Notably, the impact of these circulating markers of inflammation on cardiovascular deaths was independent of traditional risk factors. Asymmetric dimethylarginine (ADMA), an endogenous inhibitor of nitric oxide-synthase, an independent predictor of endothelial dysfunction and poor cardiovascular outcome, is increased in patients with advanced CKD [29–33]. The combination of inflammation, malnutrition (low serum albumin) and atherosclerosis was recently incorporated into the term

protein–energy wasting (PEW), which has been put forth as a leading cause for the excess mortality in patients with end-stage CKD [19,24,28]. In this regard, a recent clinical trial of apparently healthy men and women with intact renal function and no hyperlipidemia but with elevated high-sensitivity C-reactive protein levels was terminated early because statin therapy significantly reduced the incidence of major cardiovascular events [34•]. The study underscored the prediction that the benefits of enrollment that were based on elevated high-sensitivity C-reactive protein were double those predicted by studies with enrollment based on elevated LDL cholesterol. Such observations emphasize the growing support for a critical role of inflammation in atherogenesis and may be especially pertinent in the chronically pro-inflammatory condition that characterizes CKD. Indeed, a recent study found that high sensitivity C-reactive protein can predict all-cause mortality in nondialysis CKD patients, that is, independent of age, estimated GFR, left ventricular mass index and vascular disease [35•].

CKD also leads to mineral–bone disorders. Laboratory abnormalities, including phosphate retention, elevated parathyroid hormone, and low 1,25-dihydroxy vitamin D levels have been extensively documented [36]. Clinical studies show that excess phosphate influences mortality and myocardial infarction in CKD patients [37,38•]. Sevelamer, a phosphate binder, delays progression of not only vascular calcification but also atherosclerotic lesion with decreased serum phosphate levels and oxidative damage in vascular intima of apolipoprotein E (apoE) - deficient mice, although in humans, benefits of such interventions may also reflect reduction in serum lipid levels [39]. Vitamin D also contributes to the regulation of renin–angiotensin system, inflammation and inhibits both cardiac hypertrophy and myocyte proliferation [40]. Although there are a number of recent studies that associate one or more of these mineral metabolism disturbances with excessive CVD in CKD, none have been definitive.

Dyslipidemia in chronic kidney disease

Among the risk factors for atherosclerotic CVD, hyperlipidemia is key; it is also the primary target for therapeutic intervention. CKD causes dyslipidemia. The magnitude and characteristics of the dyslipidemia depends on the degree of renal impairment, the etiology of the primary renal disease, and presence of nephrotic syndrome [41,42•,43]. CKD without nephrotic syndrome is typified by elevated triglycerides, low high-density lipoprotein (HDL) and total cholesterol concentration that is, at, or near, normal levels (Table 1). Although this dyslipidemic pattern does not necessarily fit into recommendations for therapeutic interventions in the general population, it belies profound disturbances in lipid metabolism. These disturbances result from overproduction as well as impairment in the clearance of apolipoproteinB (apoB)-containing lipoproteins that reflects abnormalities in lipid substrates, enzymes, lipid transfer proteins and lipoprotein receptor activity (Table 1).

Hypertriglyceridemia is an early feature of CKD. It persists at every stage of renal dysfunction, and is found in the majority of patients with ESRD, particularly diabetics and those undergoing peritoneal dialysis. Hyper-triglyceridemia reflects increased synthesis by the liver and especially decreased clearance because of decreased activity of lipolytic enzymes, including lipoprotein lipase and hepatic lipase, and reduction in their inhibitors, such as pre β HDL, reduced apolipoprotein CII and apoE [41]. Elevation of triglyceride-rich lipoproteins also reflects upregulation of hepatic acyl-CoA cholesterol acyltransferase (ACAT) [43]. Decreased catabolism also leads to accumulation of small dense low-density lipoprotein (LDL) particles. The impaired catabolism, at least in part, reflects posttranslational modification of apolipoproteins by CKD-related oxidation, glycation, carbamylation, [44–46]. In addition, there is reduced receptor-mediated uptake of triglycerides by hepatic LDL-receptor related protein (LRP) and VLDL-receptors [41,43].

As noted, increased CVD in CKD is not because of higher levels of cholesterol. Clinicians have also been reluctant to initiate lipid-modulating therapy because of the possibility of toxicity. Until very recently, patients with renal impairment were specifically excluded from studies of treatment strategies, further limiting assessments of treatment efficacy in this population. Nonetheless, recent subgroup analysis of some secondary prevention trials, including, Cholesterol and Recurrent Events (CARE), Heart Protection Study (HPS), and Veterans' Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) found that lipid lowering agents are effective in preventing cardiovascular events in patients with mild-to-moderate CKD; however, other studies did not confirm these findings, that is, Prevention of Renal and Vascular End Stage Disease Intervention Trial (PREVEND IT) [47–50]. Interestingly, intensive lipid lowering therapy (atorvastatin 80 mg/day versus 10 mg/day) was found to be more beneficial in patients with mild-to-moderate CKD than in individuals with normal or near-normal renal function although some of the reduction in cardiovascular risk may reflect improvement in renal function observed in patients on the higher statin dose [51••].

By contrast to mild–moderate CKD, patients with advanced or end-stage kidney disease who are at the greatest risk for cardiovascular events show an inconsistent relationship to elevated lipids and have even been found to have ‘reverse epidemiology’ with increased mortality with lower cholesterol levels [20–22,52]. This paradoxical effect has been linked to protein energy wasting and/or inflammation that characterize CKD [22]. Notably, in a study of more than 15 000 ESRD patients, adjustments for malnutrition and inflammation did not improve the association between mortality and low cholesterol levels [53]. Moreover, the effects of therapeutic interventions that lower LDL are equivocal as renal damage progresses. Thus, some but not all observational studies found that lowering LDL reduced relative risk in total mortality in ESRD patients [54–57]. The only prospective randomized controlled clinical trial evaluated 1200 hemodialyzed diabetics over a period of 4 years and found that atorvastatin which decreased the serum cholesterol had a nonsignificant 8% relative risk reduction on the combined primary end point of cardiac death, nonfatal myocardial infarction or stroke [57]. It has been suggested that the negative results reflect very advanced atherosclerotic disease and/or importance of other cardiovascular disorders nonmodifiable by lipid-lowering therapies.

Thus, although there is indisputable evidence that hyper-lipidemia underlies atherosclerosis and that reduction in LDL decreases coronary events and mortality in the general population and in early stages of CKD, this abnormality may be a weaker predictor as renal damage progresses. Even in the general population, LDL-lowering therapy is not uniformly beneficial. Such findings have been interpreted to suggest that a plateau of risk reduction may have been achieved with current interventions [58]. The implication of these findings has been variously interpreted [59], including the need for more aggressive reduction in LDL cholesterol, or the possible importance of inflammation in atherogenesis, or the possibility that lipid abnormalities other than serum LDL cholesterol levels modulate cardiovascular risk, such as HDL, or disturbed lipid homeostasis at the local cellular level (see below).

Decreased HDL cholesterol has long been recognized to be a powerful negative-risk factor for CVD, and has emerged as a new target for intervention in progression and even regression of atherosclerosis [60]. Low HDL is a consistent finding at all stages of CKD [41]. Impaired maturation of HDL in CKD is primary due to downregulation of lecithin–cholesterol acyltransferase (LCAT), which esterifies cholesterol taken up by HDL that enables it to acquire subsequent cholesterol particles, increased cholesteryl ester transfer protein (CETP) and ACAT, as well as decreased hepatic lipase, Table 1. Although there is currently no therapy that specifically targets HDL, some benefits of currently used LDL-lowering interventions have been ascribed to the accompanying increase in HDL levels [61]. Moreover, in a small trial evaluating the effects of a synthetic HDL-associated apolipoprotein A-I (apoA-I Milano),

there was significant regression of atherosclerotic lesions [62], providing support that targeting HDL may have important beneficial consequences for atherosclerosis.

Efforts to raise HDL have been problematic. A clinical trial with an inhibitor of CETP, torcetrapib, was terminated because of increased mortality and cardiovascular events [63••] possibly related to an off-target effect indicated by increased aldosterone. Further, the ultrasonographic assessments did not find benefit of torcetrapib on progression of coronary atherosclerosis or carotid intimal thickness [64]. Interestingly, although low HDL levels tracked with high CETP activity in patients with CKD stage V, neither parameter was associated with cardiovascular events over a 48-month period [65]. Such findings cast doubt on the potential efficacy of CETP inhibitors in CKD. In this regard, accumulating evidence suggests that the quality of HDL may be more important than the level of circulating HDL [66]. Support for this concept includes studies showing that the antiatherogenic effects of plasma HDL depend on the ability of the lipoprotein to accept cholesterol for reverse cholesterol transport and provide antioxidative and anti-inflammatory functions [67]. CKD patients have abnormalities in the maturation, composition, stability, and antioxidant capacity of HDL [46,68,69]. These considerations are especially relevant, as a number of antioxidative functions of HDL depend on enzymes and transfer proteins known to be deranged by CKD including LCAT, paraoxonase, and phospholipid transfer protein which have the possibility of not only losing the antiatherogenic properties but actually promoting inflammation, and thus atherosclerosis.

Among the mechanisms by which HDL exerts its antiatherogenic effects, a pivotal factor is thought to be HDL's involvement in reverse cholesterol transport. This is a multistep, multiorgan process, the net effect of which is to remove excess cholesterol from macrophages in peripheral tissue, transport it in plasma for delivery and processing within the liver, and excretion in bile and intestine [70,71••,72••]. CKD may confound the reverse cholesterol transport due to hepatic impairment in synthesis and function of several enzymes and lipoproteins involved in the process, such as ApoA-I, ApoE, hepatic lipase, LCAT activity (Table 1). New information suggests that the macrophage lipid homeostasis in CKD, the first step in reverse cholesterol transport, is also deranged.

Macrophage lipid homeostasis

The cholesterol loaded macrophage foam cell is the hallmark of the atherogenic lesion. Foam cell formation results not only from an unrelenting uptake of lipoproteins but failure of cholesterol export mechanisms to keep pace with internalization of cholesterol from lipoproteins and cellular debris, which is mediated by scavenger receptors (Fig. 2). Increased cholesterol uptake in the setting of renal dysfunction is predicted from observations that monocytes of patients with renal damage upregulate scavenger receptor expression [73]. However, once upregulated, macrophages do not downregulate scavenger receptors or inflow of cholesterol by this pathway, and foam cell formation becomes critically dependent on lipid efflux, which involves mobilization of excess cholesterol from intracellular pools to the plasma membrane and transfer to suitable external cholesterol acceptors [70,74•]. The key pathways for cholesterol movement out of macrophages involve an energy-dependent efflux linked to the ATP-binding cassette transporter A1 (ABCA1), ABCG1, and HDL scavenger receptor class I type 1 (SR-B1) Fig. 2 [70,71••,72••,74•].

As foam cell formation depends on perturbations in macrophage cholesterol homeostasis, we recently investigated whether renal dysfunction affects the influx of macrophages within the atherosclerotic lesion as well as the cell's lipid metabolism. Reduction in renal mass increases atherosclerosis in apoE deficient hyperlipidemic mice, which is proportional to the extent of renal ablation. We showed that uninephrectomy (UNx), which has little effect on renal function,

dramatically increases the extent of atherosclerosis and that the lesions have greater macrophage content than in mice with intact kidneys [75]. *In vitro*, macrophages of UNx mice had increased migratory response to a monocyte chemoattractant protein (MCP)-1 stimulus. These findings complement observations that reduction in renal mass can induce increased endothelial expression of adhesion molecules, including intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 and generalized oxidative stress, findings that predict enhanced monocyte adhesion and migration into the vascular intima [76,77]. Antagonism of angiotensin II (AII) is well established to benefit CVD in the general population [78]. We, therefore, examined the effect of such intervention in our mice. Although both the AII antagonist losartan and a nonspecific vasodilator hydralazine similarly decreased systemic blood pressure, only losartan decreased atherogenesis, lesional macrophage content and macrophage migration.

Our preliminary evaluation of cellular lipid homeostasis revealed strikingly increased lipid content of peritoneal macrophages of UNx mice [79,80]. The cellular lipid expansion was not simply a reflection of the *in vivo* plasma lipid environment suggesting that foam cell formation and atherosclerosis do not necessarily parallel plasma lipid levels, particularly in the presence of renal dysfunction. The studies further showed that *in vivo* treatment with losartan reduced cholesterol content in macrophages of UNx. Since cholesterol efflux in this setting is a pivotal step in determining whether intracellular lipid homeostasis is maintained or whether the macrophage will turn into a foam cell, we assessed efflux. Cholesterol efflux was significantly in macrophages from UNx mice. This effect was linked to repression of the macrophage ABCA1 transporter. Notably, *in vivo* treatment with losartan restored macrophage ABCA1 expression, results that complement previous in-vivo and in-vitro findings that exogenous AII downregulates ABCA1 [80,81,82•]. UNx macrophages had significantly elevated nuclear factor kappa B (NF- κ B) activity and specific antagonism of the NF- κ B activation pathway in macrophages lessened repression of the ABCA1 transporter. Losartan significantly decreased upregulation of NF- κ B, suggesting this as a potential key regulatory step. It is of interest that plasma from CKD patients' downregulated ABCA1 in cultured endothelial cells [83•] and that cultured human macrophages exposed to the AII receptor blocker telmisartan increased cholesterol efflux [84•]. These observations suggest a pivotal importance of ABCA1 and macrophage cholesterol homeostasis in the setting of renal dysfunction, providing a basis for possible target for excess CVD in this setting (Fig. 2). Although there is strong support for AII antagonism lessening progressive renal parenchymal damage, the impact of this intervention on CVD in CKD remains to be clarified. Post-hoc analysis of patients with early renal damage treated with angiotensin-converting enzyme inhibitors (ACEI) document fewer cardiovascular events and increased survival [85]. A 2 year follow up of 400 patients with left ventricular hypertrophy on hemodialysis found a trend for lower rate of cardiovascular events in patients treated with the ACEI, fosinopril, but the difference was not significant [86]. Although constrained by some limitations, two reports suggest that antagonism of AII actions reduces cardiovascular morbidity and mortality in hemodialysis patients [87,88].

Conclusion

Recognition of the mechanisms and risk factors of atherosclerotic disease has made a tremendous impact on morbidity and mortality in the general population. Although many of these risk factors prevail in patients with CKD, additional disturbances in lipid metabolism, inflammation and macrophage cholesterol handling contribute to the excess vascular disease, which is apparent at every level of renal impairment. Clarification of lipid abnormalities may enable more aggressive and specific therapeutic interventions. However, even available antilipidemic therapies may provide anti-inflammatory benefits in this setting. Antagonism of AII actions which predicts beneficial effects on inflammation, may also promote macrophage

efflux and subsequent elimination of lipids that offer the possibility of a novel target for lessening atherosclerosis in CKD.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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Figure 1. Deaths from cardiovascular disease in the general population and chronic kidney disease
Between 1980 and 2000, CVD mortality in the general population in the United States fell by more than 40%, whereas CVD mortality in CKD is estimated between 10 to more than 100% above the general population. CKD, chronic kidney disease; CVD, cardiovascular disease. Adapted from [12•,13,14].

Figure 2. Macrophage lipid homeostasis in chronic renal disease

CKD upregulation of scavenger receptors CD36 and SR-A enhances cholesterol uptake whereas downregulation of ABCA1 transporter represses cholesterol efflux that promotes foam cell formation. CKD induces oxidative stress, inflammatory cytokines, and dyslipidemia that may regulate cellular processes involved in macrophage lipid metabolism. Rx, possible therapeutic interventions; oxLDL, oxidized light density lipoprotein; SRA, scavenger receptor A; CD36, scavenger receptor 36; ABCA1, ATP binding cassette transporter A1; ABCG1, ATP binding cassette transporter G1; SRB1, scavenger receptor B1; ApoA1, apolipoprotein AI; HDL, high density lipoprotein; LXR, liver X receptor; RXR, retinoid X receptor; PPAR, peroxisome proliferator-activated receptor; NFκB, nuclear factor kappa B.

Table 1

Common feature of serum lipids, lipoproteins, apolipo-proteins, enzymes, and transfer proteins in predialysis chronic kidney disease patients

	CKD stage 1–4	CKD stage 5	Nephrotic syndrome
Total cholesterol	↔	↔	↑
Triglyceride	↔ or ↑	↑	↑
LDL-cholesterol	↔ or ↑	↔ or ↓	↑
Small dense LDL	↑	↑	↑
HDL-cholesterol	↓ or ↔	↓	↓ or ↔
Lipoprotein a	↑	↑	↑
ApoA-I, A-II	↓	↓	↑ or ↓
ApoC-II	↓	↓	↑
ApoC-III	↑	↑	↑
ApoE	↓	↓	↑
LPL activity	↓	↓	↓
Hepatic lipase activity	↓	↓	↓
ACAT	↑	↑	↑
LCAT activity	↓	↓	↓
CETP	↑	↑	↑

ACAT, acyl-CoA cholesterol acyltransferase; Apo, apolipoprotein; CETP, cholesterol ester transfer protein; CKD, chronic kidney disease; HDL, high density lipoprotein; LCAT, lecithin cholesterol acyltransferase; LDL, low density lipoprotein; LPL, lipoprotein lipase.