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Narrative Review

Cholesterol Metabolism in CKD

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Patients with chronic kidney disease (CKD) have a substantial risk of developing coronary artery disease. Traditional cardiovascular disease (CVD) risk factors such as hypertension and hyperlipidemia do not adequately explain the high prevalence of CVD in CKD. Both CVD and CKD are inflammatory states and inflammation adversely affects lipid balance. Dyslipidemia in CKD is characterized by elevated triglyceride levels and high-density lipoprotein levels that are both decreased and dysfunctional. This dysfunctional high-density lipoprotein becomes proinflammatory and loses its atheroprotective ability to promote cholesterol efflux from cells, including lipid-overloaded macrophages in the arterial wall. Elevated triglyceride levels result primarily from defective clearance. The weak association between low-density lipoprotein cholesterol level and coronary risk in CKD has led to controversy over the usefulness of statin therapy. This review examines disrupted cholesterol transport in CKD, presenting both clinical and preclinical evidence of the effect of the uremic environment on vascular lipid accumulation. Preventative and treatment strategies are explored.
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INDEX WORDS: Cholesterol transport; chronic kidney disease (CKD); atherosclerosis; high-density lipoprotein (HDL); low-density lipoprotein (LDL); inflammation; dyslipidemia; cardiovascular disease (CVD); uremic toxins; reactive oxygen species (ROS); lipid-lowering therapy; statin therapy; nontraditional risk factor.

Chronic kidney disease (CKD) affects approximately 10% to 13% of the general population. CKD accelerates the development of atherosclerosis and increases the risk of cardiovascular disease (CVD).[1,2] CVD is the primary cause of morbidity and mortality in these patients. Most patients with CKD die of cardiovascular events before reaching end-stage renal disease (ESRD).[3] Cardiovascular damage starts early in the progression of kidney disease. Even mildly decreased glomerular filtration rates (GFRs) or moderately increased albuminuria (microalbuminuria) may be independent predictors for CVD or stroke.[4,5] The incidence and severity of CVD increase as GFR declines.[6] While Framingham risk factors, including hypertension, hypercholesterolemia, and diabetes mellitus (DM), are common in patients with CKD (Fig 1), they do not fully account for the magnitude of CVD risk in CKD.[7-9] Exhaustive interventions to improve risk profile, such as controlling levels of low-density lipoprotein (LDL) cholesterol or C-reactive protein (CRP), fail to improve cardiovascular outcomes.

Nontraditional risk factors probably help promote the development of atherosclerosis in the presence of decreased kidney function[10,11] (Fig 1). These include inflammation, uremic toxins, oxidative stress, carbamylation, nitric oxide (NO) depletion, hyperhomocystinemia, and altered metabolism of lipids, calcium, and phosphate.[12,13] Endothelial dysfunction is a common feature of CKD that occurs early and is a predictor of CVD.[14,15]

Pathology studies have demonstrated that coronary atherosclerosis and calcification are more frequent and advanced in patients with CKD compared with patients without CKD.[16,17] Soft tissue mineralization in the form of arterial calcification is a marker of atherosclerosis and a strong predictor of cardiovascular events.[18] A recent imaging study comparing nonculprit coronary atherosclerotic plaques from patients with and without CKD in the Massachusetts General Hospital Optical Coherence Tomography Registry showed more prevalent calcification and cholesterol crystals in plaques of patients with CKD.[19] Cholesterol crystals trigger inflammation and destabilize plaque. Greater severity of atherosclerosis in patients with CKD may be associated with impaired lipid and calcium-phosphate metabolism.

Atherosclerosis is thought to be accelerated in CKD due to the accumulation of atherogenic oxidation-prone lipoproteins and small dense LDL particles, along with high-density lipoprotein (HDL) paucity and qualitative dysfunction, oxidative stress, and inflammation. This review considers the multiple lipid-related mechanisms that contribute to cardiovascular risk in CKD beyond serum cholesterol levels.

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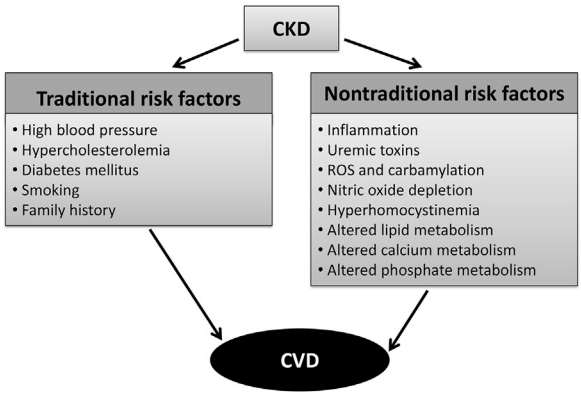

Figure 1. Chronic kidney disease (CKD) and cardiovascular disease (CVD) risk factors and their interplay. Traditional risk factors are found in both the CKD and non-CKD population. Nontraditional risk factors may result from or be worsened by CKD and negatively affect the cardiovascular system in the CKD population. Abbreviation: ROS, reactive oxygen species.

THE LIPID PROFILE IN CKD AND ITS RELATIONSHIP WITH CVD

Dyslipidemia is common in CKD. Epidemiologic studies have shown that the incidence of CKD is associated with increased plasma triglyceride and very LDL (VLDL) cholesterol levels, as well as decreased HDL cholesterol levels.[20,21] Intermediate-density lipoproteins and chylomicron remnants may accumulate. Total and LDL cholesterol levels are often within normal limits or somewhat reduced.[22] LDL cholesterol levels are less predictive of cardiovascular risk in CKD, especially in those with lower GFRs. Despite this, the benefit of lipid lowering in this population has been demonstrated.[23,24] While total cholesterol in the general population is linked to the risk for developing and dying of CVD, data from the CKD population have been less clear. A reverse epidemiology phenomenon has been found in dialysis patients, with lower cholesterol levels associated with higher mortality rates, possibly reflecting the profound malnutrition and inflammatory status present in this population.[25] While these findings with advanced kidney disease and ESRD collectively suggest alterations in atherogenic mechanisms compared with the general population, the discussion here focuses on patients with non–dialysis-dependent CKD because the underlying processes may not be identical in dialysis patients compared with those with earlier stages of kidney disease.

Perhaps more important than any quantitative change in cholesterol level is the alteration in lipoprotein structure. Lipoproteins found in patients with CKD are disproportionately modified with LDL that is enriched in triglycerides and an increased proportion of small-dense LDL (Table 1). LDL is composed of a heterogeneous range of particles with variable atherogenic potency. LDL particles vary in size, buoyant density, and structure. Small dense LDL is believed to be markedly proatherogenic, and this is attributed to its ability to infiltrate the vessel wall and its increased susceptibility to oxidative modification.[26-30] Small dense LDL is able to breach the endothelial monolayer and bind to proteoglycans of the extracellular matrix in the arterial intima.[31] The small dense LDL particles then remain trapped in the intima, where they can be oxidized by NADPH (reduced nicotinamide adenine dinucleotide phosphate) oxidases or myeloperoxidase or by nonenzymatic oxidation. Studies link small dense LDL to CVD risk even with normal total LDL levels.[32,33] Shoji et al[34] demonstrated that small dense LDL is a clinically relevant marker of carotid atherosclerosis

Table 1. The Lipid Profile in CKD

Type of Lipid Abnormality	Implication in Atherosclerotic CVD	Reference
Presence of small-dense LDL	Small dense LDL are highly susceptible to oxidative modification and serve as a marker of carotid atherosclerosis	25-36
Decreased endothelium-bound LPL levels	Decreased clearance of remnant LDL: VLDLs are not converted to IDLs and LDLs and accumulate in the bloodstream; this results in increased systemic LDL and elevated cholesterol and triglyceride levels	20-22, 35-40
Elevated Lp(a) level	Lp(a) accumulates in the vascular wall in atherosclerotic lesions and is resistant to lipid-lowering drugs; elevated Lp(a) level is an independent risk factor for CVD	41-44
Upregulated HMG-CoA reductase and ACAT-2 activity	Promotes accumulation of cholesterol esters in the fat droplets, reduced capacity to absorb cholesterol, and overproduction of Apo-B–containing lipoproteins (LDL, VLDL)	49-52
Reduction in LCAT and PON1 activity	Leads to accumulation of nascent preβ-HDL due to impaired maturation of HDL particles, conversion of lipid-rich HDL2 to lipid-poor HDL3, and limited HDL-mediated clearance of cholesterol from extrahepatic tissues	49-56, 80-82, 85, 86

Abbreviations: ACAT-2, acyl coenzyme A:cholesterol acyltransferase 2; Apo-B, apolipoprotein B; CKD, chronic kidney disease; CVD, cardiovascular disease; HDL, high-density lipoprotein; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; IDL, intermediate density lipoprotein; LCAT, lecithin-cholesterol acyltransferase; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); LPL, lipoprotein lipase; PON1, paraoxonase 1; VLDL, very low-density lipoprotein.