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REVIEW ARTICLE

Residual Cardiovascular Risk in Chronic Kidney Disease: Role of High-density Lipoprotein

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Although reducing low-density lipoprotein-cholesterol (LDL-C) levels with lipid-lowering agents (statins) decreases cardiovascular disease (CVD) risk, a substantial residual risk (up to 70% of baseline) remains after treatment in most patient populations. High-density lipoprotein (HDL) is a potential contributor to residual risk, and low HDL-cholesterol (HDL-C) is an established risk factor for CVD. However, in contrast to conventional lipid-lowering therapies, recent studies show that pharmacologic increases in HDL-C levels do not bring about clinical benefits. These observations have given rise to the concept of dysfunctional HDL where increases in serum HDL-C may not be beneficial because HDL loss of function is not corrected by or even intensified by the therapy. Chronic kidney disease (CKD) increases CVD risk, and patients whose CKD progresses to end-stage renal disease (ESRD) requiring dialysis are at the highest CVD risk of any patient type studied. The ESRD population is also unique in its lack of significant benefit from standard lipid-lowering interventions. Recent studies indicate that HDL-C levels do not predict CVD in the CKD population. Moreover, CKD profoundly alters metabolism and composition of HDL particles and impairs their protective effects on functions such as cellular cholesterol efflux, endothelial protection, and control of inflammation and oxidation. Thus, CKD-induced perturbations in HDL may contribute to the excess CVD in CKD patients. Understanding the mechanisms of vascular protection in renal disease can present new therapeutic targets for intervention in this population. © 2015 IMSS. Published by Elsevier Inc.

Key Words: Cardiovascular disease, Chronic kidney disease, Residual cardiovascular risk, HDL, Statins, Cholesterol efflux.

Introduction

Whereas low-density lipoprotein (LDL) continues to provide evidence of its value as a cardiovascular disease (CVD) risk marker and therapeutic target for CVD benefits, increasing knowledge of high-density lipoprotein (HDL) is casting doubts about its role in CVD risk prediction with reservations arising from recent natural randomization studies and absence of clinical trial support for its role as a therapeutic target. However, in view of the recognition establishing that HDL performs multiple important functions from extracting cellular cholesterol to toning-down inflammation and oxidation, it is possible that the key in utilizing it as risk marker or therapeutic target is not in determining levels of HDL cholesterol (HDL-C) but rather in assessing its functionality. Raising HDL-C levels may be appropriate when HDL is functional but not when HDL is dysfunctional. The difficulty is identifying HDL that is functional and developing interventions that increase its functionality. Renal disease has been known to affect HDL levels, but more recent evidence suggests that its strongest effect is in influencing HDL composition and affecting its functions.

CVD in Renal Patients

Chronic kidney disease (CKD) is an independent risk factor for CVD. The American College of Cardiology/American Heart Association (ACC/AHA) and the National Kidney

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Foundation (NKF) recommend that CKD be considered equivalent to pre-existing coronary artery disease (CAD) as risk predictor (1,2). Using a large population-based study, Go et al. first documented that a decline in the glomerular filtration rate (GFR) is the main independent risk factor for CV events including hospitalization secondary to peripheral artery disease (PAD), CAD, congestive heart failure (CHF), or stroke (3). Similar conclusions were drawn from a systematic review encompassing ~1.4 million adults showing that a gradual fall of GFR is associated with an increased risk of death, and that individuals with lowest baseline GFR are at the highest risk of all-cause mortality (4). CKD not only increases CVD prevalence but also conveys poorer prognosis after CV events. Compared to non-CKD patients whose in-hospital mortality is ~2%, individuals with modest reduction in GFR (50–75 mL/min) have 6% mortality, those with GFR 35–50 mL/min have 14% mortality, those with GFR of <35 mL/min have 21% mortality, and those requiring dialysis have a 30% mortality rate (5). Other studies confirm the dramatically decreased survival of CKD patients following acute myocardial events, estimating that the risk of sudden cardiac death is increased by 11% for every 10 mL/min decline in GFR (6). In individuals with established ESRD, only half are expected to survive an acute CV event (4,7). Compared to age-adjusted CVD mortality in the non-CKD population, this estimate is 15–30 times higher, a discrepancy that increases among younger CKD cohorts (8). Importantly, although prevention of progressive deterioration in kidney function has been the primary concern in CKD, it is now clear that acute cardiovascular events and death are more common than CKD progression to ESRD. In a study of ~30,000 CKD patients, the 5-year CVD mortality rate was 19.5%, 24.3%, and 45.7% in those with CKD stages 2, 3, or 4, respectively, compared with a much lower risk of progressing to ESRD (1.1%, 1.3%, and 19.9%, respectively) (9). This is significant because early CKD now affects some 10–16% of the population worldwide, a figure that is projected to rise (10,11).

Recent studies underscore that cardiovascular mortality in CKD is due to many causes including myocardial dysfunction, valvular disease, and arrhythmias; however, atherosclerotic CAD is significantly higher in CKD patients than in the general population (12,13). Even early kidney disease has been linked to early signs of atherosclerosis including subendothelial lipid deposition, upregulation of adhesion molecules, recruitment of monocytes, conversion of macrophages to foam cells, and elastolysis (14,15). The prevalence as well as the progression of atherosclerotic disease is increased in the CKD population. Thus, CKD patients with an initially normal angiography develop myocardial infarction (MI) more frequently than non-CKD subjects (5.2 vs. 0.7%), whereas >50% of ESRD patients on dialysis develop significant new coronary stenosis (>50%) over a period of 30 months (16). Approximately 10–20% of CAD deaths in dialysis patients are due to acute MI, with a third occurring in the first year of dialysis treatment (17,18). Overall, atherosclerotic CAD is a significant cause of morbidity and mortality over the entire spectrum of CKD, and GFR <60 mL/min is as good at predicting future cardiac events as are previous history of MI, diabetes, angiographic evidence of obstructive CAD, and a positive stress test (16). This is a challenging circumstance because the presentation of acute CVD event in advanced CKD patients is often atypical, carries a poor prognosis, and is constrained by limited therapeutic options.

Traditional and Nontraditional Risk Factors and Residual Cardiovascular Risk

Traditional CVD risk factors described in the Framingham study (19) include dyslipidemia, diabetes mellitus, hypertension, smoking, older age, male gender, physical inactivity and family history of premature CVD. All these risk factors are common in CKD. However, it is not known the extent to which each factor adds to the incidence of CVD in CKD patients. For example, elevated levels of LDL-C, the primary driver of CVD in the general population, are not consistently present in CKD. Indeed, the degree and pattern of dyslipidemia are not uniform across CKD stages and are heavily influenced by the degree of renal dysfunction, the underlying etiology, and whether nephrotic syndrome is present (Table 1). For example, nephrotic patients are characterized by dramatically increased total and LDL-C, high triglycerides and normal or decreased HDL-C. Non-nephrotic CKD patients typically have normal or increased total and LDL-C, high triglycerides and decreased HDL-C. Patients whose C KD has advanced to ESRD on hemodialysis have normal or decreased total and LDL-C, high triglyceride and decreased HDL-C, whereas ESRD patients on peritoneal dialysis have increased total and LDL-C, very high triglycerides and decreased HDL-C (20,21). The paradoxical divergence between LDL-C levels and CVD becomes particularly apparent as renal dysfunction progresses to ESRD (22–24). Other risk factors relevant in the general population such as hypertension and increased BMI also lose their

Table 1. Lipid and apolipoprotein profile across CKD

	Pre-dialysis CKD	Nephrotic syndrome	Hemodialysis	Peritoneal dialysis
Total cholesterol	→↑	↑↑	→↓	↑
LDL cholesterol	→↑	↑↑	→↓	↑
Small dense LDL	↑	↑	↑	↑
ApoB	→	↑↑	↓→↑	↑
HDL	↓	→↓	↓	↓
Triglyceride	↑	↑	↑	↑↑
Lp(a)	→↑	↑↑	↑	↑↑
ApoA-I	→↓	→↑	↓	↓

CKD, chronic kidney disease; LDL, low-density lipoprotein.

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