Treatment of Hyperlipidemia Changes With Level of Kidney Function—Rationale

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Abstract: Lipoprotein abnormalities such as low levels of high-density lipoprotein (HDL) and high triglycerides (TGs), associated with the metabolic syndrome, are also associated with subsequent decline in kidney function. Patients with end-stage kidney disease also exhibit low HDL and high TGs and a modest reduction in low-density lipoprotein (LDL), although the mechanisms responsible for these changes differ when patients with end-stage kidney disease are compared with those having metabolic syndrome with normal kidney function, as do lipoprotein structures. Among dialysis patients, oxidized LDL, levels of TG-rich intermediate-density lipoprotein, and low HDL are associated with aortic pulsewave velocity and other markers of atherosclerosis. Statins are effective in reducing LDL and do decrease risk of cardiovascular events in patients with CKD not requiring dialysis but have no significant effect on outcomes, including all-cause mortality among dialysis patients. Similarly gemfibrozil and other fibrates lower TGs, increase HDL, and reduce cardiovascular events, but not mortality, among patients with CKD not requiring dialysis but have no significant effect on cardiovascular outcomes in dialysis patients. There is potential clinical benefit in treating elevated LDL, TGs, and low HDL in patients with CKD using statins or fibrates in those not yet requiring dialysis.
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LIPOPROTEINS AND THEIR CONTRIBUTION TO CARDIOVASCULAR DISEASE AT DIFFERENT STAGES OF CHRONIC KIDNEY DISEASE

Cardiovascular disease is the leading cause of death in patients with CKD.[1] The relative risk of mortality from cardiovascular disease increases as glomerular filtration rate declines.[2] Although low-density lipoprotein (LDL) cholesterol level is associated with increased mortality in the general population[3] among dialysis patients, LDL is negatively associated with cardiovascular mortality.[4-6] The purpose of this article is to review recent research on lipids in CKD and to provide a framework of treatment based on different stages of CKD, where applicable.

Relationship Between Lipid Disorders and Outcomes

In the general population, there is a strong, graded association between LDL cholesterol levels and subsequent cardiovascular mortality in patients with and without pre-existing cardiovascular disease.[7-9] The risk of cardiovascular disease (CVD) increases with decreasing levels of glomerular filtration rate (GFR).[2] How much of this risk is related to dyslipidemia in the CKD population is a matter of debate. Muntner and colleagues,[10] using the Atherosclerosis Risk in Communities database, showed that in patients with CKD, risk of coronary heart disease is related to total cholesterol and triglyceride (TG) levels. On the other hand, in a study of elderly CKD patients, with mild-moderate reductions in GFR (mean GFR 50 mL/min/1.73 m^2), no such association was found.[11]

Using the African American Study of Kidney Disease and Hypertension Trial cohort (African American predialysis patients with estimated GFR [eGFR] between 20 and 65 mL/min/1.73 m^2), when subjects were stratified by the presence or absence of malnutrition or inflammation (M-I), the non-M-I group exhibited a positive association between CVD and cholesterol levels. This was not so in the group with malnutrition or inflammation who had greater CVD risk but no association between cholesterol level and CVD outcomes.[12] This finding was corroborated in a study of Veteran Affairs patients with CKD, where case-mix and the malnutrition-inflammation syndrome attenuated the association between lipid levels and mortality.[13] Finally, in a study by Tonelli and colleagues of 836,060 adults from the Alberta Kidney disease network, although the absolute risk of myocardial infarction was higher in patients with lower eGFR, the association of myocardial infarction with higher LDL levels was weaker.[14] In summary, the weight of the evidence points against total and LDL cholesterol being a good predictor of cardiovascular risk in patients with CKD.

LIPOPROTEIN DISORDERS ASSOCIATED WITH DECREASED GLOMERULAR FILTRATION RATE

Kidney functional decline is associated with increased risk for low HDL independently of obesity measured as body mass index.[15] The risk of having a low HDL level is primarily increased among nonobese individuals but not among subjects with significantly increased body mass index.[15] TG levels are associated with adiposity in patients with kidney failure; however, LDL cholesterol is not.[16] Disordered lipid metabolism among patients who are on dialysis is both qualitatively and quantitatively different than those with normal kidney function and suggests that the causative relationship between LDL cholesterol

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and cardiovascular outcomes either differs qualitatively as GFR declines or that other non-lipid-related processes overwhelm the effect of LDL cholesterol. The disorder in lipid metabolism in patients with advanced CKD is more of a dyslipidemia rather than hyperlipidemia (Table 1).[17]

In obese subjects with normal kidney function, increased TG level is primarily caused by increased hepatic synthesis of very low-density lipoprotein (VLDL)[18,19] and chylomicrons by the gut.[20-23] The VLDL produced is the TG-rich VLDL1, a precursor of the more atherogenic small LDL particles.[24] TGs are transferred to peripheral, muscle, and adipose tissue, although their capacity to take up and metabolize TGs is impaired.[25] The TG-rich core is transferred to maturing HDL in exchange for cholesterol esters as a consequence of increased activity of the enzyme cholesterol ester transfer protein (CETP). This then creates LDL and a TG-rich HDL that is then acted on by hepatic lipase (HL), the activity of which is also increased in metabolic syndrome (MS). The combined action of CETP and HL increases the proportion of HDL in the smaller HDL_3 isoform that is cleared more rapidly, in part by the kidney.[18,26] The decrease in HDL levels in this case is a consequence of increased clearance rather than decreased production. HDL turnover is actually increased.[27-29] Increased LDL synthesis in MS is linked to the increased production of VLDL and more rapid clearance of HDL.

Low HDL levels are associated with obesity, insulin resistance,[30] and CKD.[31] The contribution to this by obesity decreases as a function of residual kidney function.[15] As GFR declines, insulin sensitivity decreases[32] providing a possible link between insulin resistance and the dyslipidemia of CKD. Both the MS and CKD are associated with an increase in the concentration of small dense LDL.[33,34] Among patients with ESRD, total LDL cholesterol is reduced compared with the general population in contrast to those with MS with normal kidney function.

CLINICAL SUMMARY

- Patients with CKD have high risk of cardiovascular disease, but it is unclear how much of this is mediated by traditional risk factors, such as hyperlipidemia.
- Statin therapy and fibrates have been shown to reduce cardiovascular events in patients with CKD not on dialysis, and use in this population should follow current guidelines for the general population at risk of cardiovascular disease.
- Presently, there is no strong evidence to recommend statin or other lipid-lowering therapy for patients on dialysis.

Lipoprotein Structure Associated With Kidney Failure

HDL is a complex accumulation of lipids and proteins. Although the principal apolipoprotein associated with HDL is apolipoprotein A I (Apo A I), HDL also may contain variable amounts of apolipoprotein A II and apolipoproteins E, C I, C II, and C III. In addition, the acute phase protein serum amyloid A may be associated with HDL or may actually replace apo A I on HDL when patients are inflamed.[35] This produces "inflammatory" HDL, which has quite different biologic properties than does Apo A I-associated HDL, in that it may actually transport cholesterol to macrophages rather than participate in reverse cholesterol transport.[36]

Failed or incomplete maturation is responsible for low HDL levels in patients with stage 5 CKD. Synthesis of HDL or at least the isoform that is associated with its most common apolipoprotein, Apo A I, is initiated by synthesis of Apo A I in the liver and intestine (Fig 1). Apo A I then engages the ATP-binding cassette (ABCA1) on macrophages on the vascular endothelium,[18,37,38] accumulating cholesterol, forming nascent pre-β HDL. Maturation of pre-β HDL into HDL_3 requires the action of lecithin cholesterol acyl transferase (LCAT) that esterifies cholesterol contained in pre-β HDL. This allows the more lipophilic cholesterol ester to form the lipotropic core of HDL_3 changing the disc-like structure of pre-β HDL into the spherical HDL_3 particle. It should be noted that HDL_3, but not pre-β HDL (or the more mature and large HDL_2 particle), carries the antioxidant enzymes, aryl hydrocarbon hydrolase, and paraoxinase1 (PON1), which are responsible for much of the antioxidative activities of HDL.[39]

HDL_3 normally continues as a substrate for LCAT and is matured then to larger HDL_2. HDL_2 then may directly engage with the scavenger receptor B-1 (SRB-1) in the liver[40] completing the cycle of reverse cholesterol transport or instead may exchange the cholesterol ester-rich core for TGs contributed by VLDL remnants producing LDL and TG-rich HDL particles.[40] TG-rich HDL is thermodynamically unstable, decreases in size, and returns to the pool of small dense HDL_3 or pre-β HDL.[41] Pre-β HDL is filtered by the kidney and taken up by the proximal tubule[42] (Fig 1).

Although the portion of HDL found in the pre-β HDL is quite small in individuals with normal kidney function, pre-β HDL, which carries none of the antioxidative enzymes normally found in HDL, represents approximately 50% of the HDL found in dialysis patients.[31] This proportion is even higher among dialysis patients with normal or increased HDL levels.[31] The ability of HDL from dialysis patients to inhibit oxidation of LDL is also reduced, likely as a consequence of this disorder in HDL distribution and structure.[39,43] Thus, oxidation, or oxidative stress, offers a potential therapeutic target for reducing cardiovascular risk in CKD.

LCAT activity is significantly reduced in dialysis patients reducing the rate of HDL maturation, in contrast to what is observed in subjects with MS with normal kidney function, who actually have an increased flux of HDL with increased levels of CETP and HL. CETP activity in patients with CKD is unchanged[44] and HL is reduced.[45] LCAT levels decrease with increasing vintage among dialysis patients.[46]

Thus, low HDL levels in MS (in the absence of kidney failure) is associated with increased apo A I synthesis and increased maturation of HDL with increased CETP and HL activities. There is increased cycling of TGs from VLDL remnants into HDL combined with