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CKD-induced dysfunction of HDL

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Abstract

Traditional risk factors do not account for increased cardiovascular disease in patients with chronic kidney disease (CKD), particularly individuals whose CKD has progressed to end-stage kidney disease requiring dialysis. CKD patients on dialysis show little to no cardiovascular benefits from lipid-lowering therapy and thus have an exaggerated residual cardiovascular risk. High density lipoprotein (HDL) quantity and functionality may explain some of the residual risk. CKD affects the composition and disrupts the functionality of HDL, including cholesterol acceptor function and inflammatory effects. Notably, although these HDL abnormalities prevail in CKD, they do not track together and thereby support the idea of separate and distinct mechanistic pathways for each critical function of HDL. Targeting individual perturbations in HDL function represents a novel approach to therapy in this population.

Keywords

HDL; Chronic Kidney Disease

Cardiovascular disease in chronic kidney disease: Incidence

Chronic kidney disease increases the risk of cardiovascular disease (CVD). [1–3] Individuals with early CKD have a natural history that predicts death from CVD is a more likely consequence than progression to ESRD and distinguishes the CKD patients as among the highest-risk cohorts for cardiovascular events of any studied population. [4] These observations are significant because early CKD now affects some 10–16% of the population world-wide, a figure that is projected to rise. [5, 6] Although cardiovascular mortality in CKD is due to many causes, atherosclerotic coronary artery disease is persistently overrepresented at every CKD stage. [7]

Traditional, non-traditional and residual risks

Traditional risk factors, including hypertension and diabetes mellitus are common across the entire CKD spectrum. However, even after statistical adjustments for these risks, CKD

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independently predicts CVD morbidity and mortality. Tonelli et al compared coronary artery events in individuals with diabetes and individuals with CKD. [8] The incidence of myocardial infarction was similar in diabetics and persons with CKD stage 1–4, but without diabetes. Thus, in addition to the traditional risk factors, CKD per se is a powerful independent risk for future coronary events and mortality. A recent report of almost 4000 individuals > 45 years of age found that recurrent coronary events associated with CKD is similar or greater than established high risk factors such as diabetes, metabolic syndrome, and cigarette smoking. [9] Such observations have led to a search for non-traditional risks specific to CKD; malnutrition, low albumin, inflammation, oxidant stress, anemia, hyperhomocysteinemia, and dysregulation of calcium/phosphorus metabolism have all been proposed; but none has been found to be causal.

Hyperlipidemia, one of major traditional risks of CVD in the general population, is not consistently elevated in CKD. Interestingly, while abundant evidence confirms LDL-C lowering by various HMG-CoA reductase inhibitors (statins) reduces CVD in the general population, a substantial residual cardiovascular risk remains and had been estimated to be ~70%. [10] This residual risk was revealed to be even greater in CKD (>80%), with the ESRD population showing remarkable recalcitrance to therapeutic reduction in residual risk. [11–13] These findings suggest that the uremic environment limits responsiveness to lipid-lowering therapy and reflects greater contribution of factors underlying the residual risk, including reduced level/function of HDL. [14–16]

CKD affects composition and function of HDL

A key mechanism by which HDL exerts its anti-atherogenic effects is reverse cholesterol transport (RCT), a multi-step, multi-organ process to remove excess cholesterol from peripheral cells transport it to the liver for catabolism and excretion into bile. [17] Modulation of the first step in RCT, namely, cholesterol efflux, can affect atherosclerotic plaques in animal models; whereas impairment in HDL's capacity to promote cholesterol efflux from cultured macrophage foam cells has been shown to predict subclinical atherosclerosis (increased carotid artery intima-media thickness in healthy volunteers) and likelihood of coronary artery disease (angiographic coronary artery disease in a case-control study) in a non-CKD population. [16] Importantly, these results occurred independently of HDL-C or apoAI levels. Aside from transport of excess cholesterol, HDL is a key modulator in other processes relevant to atherogenesis such as inflammation and oxidant stress. [15] HDL also protects and supports the endothelium through inhibition of monocyte chemotaxis, adhesion molecule expression, enhanced nitric oxide, and prostacyclin production. HDL promotes anticoagulation, augments urokinase-dependent fibrinolysis while inhibiting platelet activation/aggregation. [15]

We examined the inflammatory and lipid-handling functions of HDL from patients with ESRD on maintenance hemodialysis (ESRD-HD). [14] HDL from ESRD-HD was dramatically less effective than normal HDL in accepting cholesterol from macrophages (median 6.9% with interquartile range vs control 14.9% [, $P<0.001$). The profound efflux impairment was also seen in ESRD-HD diabetics compared with diabetics without kidney disease (median 8.1% vs control 13.6%, $P=0.009$). The efflux remained significantly lower

in ESRD-HD patients after adjustment for age, sex, race, body mass index, high sensitivity CRP, total cholesterol, triglycerides, serum HDL level, serum LDL level, cardiovascular disease, and use angiotensin converting enzyme-inhibitor/angiotensin II receptor blocker (ARB). Strikingly, HDL cholesterol acceptor capacity impairment in ESRD-HD patients persisted irrespective of the serum HDL-C level (Figure 1). These results illustrate that HDL-C levels may be a poor surrogate for cholesterol efflux capacity in the ESRD-HD.

Statin use did not improve efflux capacity to HDL from ESRD-HD. The results complement the confounding data that the interventions with statins provide only limited benefits against acute events in the ESRD-HD population even in the face of robust reduction in LDL-C. [11–13] Interestingly, activation of cellular transporters by liver X receptor (LXR) agonist that increased expression of the cellular transporter, ATP-binding cassette A1 (ABCA1) and G1 (ABCG1) increased cholesterol efflux to HDL from ESRD-HD as well as from control subjects. These findings raise the novel possibility that, even in the face of dysfunctional HDL that characterizes advanced CKD, activation of cellular transporters may abrogate pro-atherogenic pathways. Holzer reported that efflux from cholesterol-loaded SR-BI overexpressing Chinese hamster ovary cells to uremic HDL had significantly reduced efflux, suggesting impairment in this transport pathway. [18] The same group also showed that albumin from dialysis patients interferes with HDL binding to the SRBI receptor which was linked to the MPO-specific oxidation product, 3-chlorotyrosine content of albumin and the cholesteryl ester:phospholipid composition of the HDL. [19] These findings raise the novel possibility that, even in the face of dysfunctional HDL that characterizes advanced CKD, activation of cellular transporters may abrogate pro-atherogenic pathways. Whether such intervention can lessen CVD risk in this population remains to be clarified.

Using the same HDL samples, we examined the cellular inflammatory response in macrophages exposed to HDL of ESRD-HD or non-CKD controls. Compared with the cytokine response in THP-1 cells treated with control HDL, HDL isolated from ESRD-HD caused a significantly greater inflammatory response in interleukin-1 β (IL-1 β), interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α). In addition to enhancing cytokine gene expression, the HDL of ESRD-HD had impaired anti-chemotactic function. These observations are in line with the understanding that CKD is a proinflammatory/pro-oxidant state. Systemic markers of inflammation and oxidant stress increase as renal function declines. [20] CKD has been shown to specifically impair the anti-inflammatory functions of HDL. [21, 22] In a prospective study >400 dialysis patients, Honda et al recently showed that ESRD-HD patients with a combination of high oxidized HDL and high IL-6 have a significantly greater increase in CIMT as well as increased risk for CVD events and CVD-related mortality. [23] Together, these findings suggest the HDL particle may be an important determinant for anti-atherogenic processes in CKD, as well as presenting a new therapeutic target.

It is interesting that in contrast to its effects on cholesterol efflux, therapy with statin abolished the difference in the cytokine response between HDL isolated from dialysis patients and non-CKD control subjects. [14] Thus, IL-1 β , IL-6 and TNF- α response to HDL from the subgroup of ESRD-HD patients on statin therapy was not different from that of controls taking statins. These results underscore the possibility that the inflammatory effects

of uremic HDL respond to statin therapy but that this effect is not linked with HDL's cholesterol handling. The divergence in HDL's inflammatory and lipid handling response to statin therapy prompted us to examine the association between anti-inflammatory and lipid-handling properties of a given HDL sample across the entire study population. We found no correlation between individual macrophage cholesterol efflux capacity of HDL and inflammatory response of macrophages within ESRD-HD subjects. It is important to underscore that the results raise the intriguing possibility of separate and distinct mechanistic pathways for different functions of HDL. This concept may explain why statins have limited benefit in this population and supports the idea that both cholesterol efflux and inflammation may have to be targeted with more specific therapies to achieve clinical improvement in this population.

CKD, specifically ESRD, affects the composition of HDL particles. Holzer et al showed that compared to HDL isolated from normal controls, the proteome of HDL from dialysis patients had increased SAA1, albumin, lipoprotein-associated phospholipase A2, and apolipoprotein C-III. [18] The lipidome of uremic HDL was also different, including reduced phospholipid but increased triglyceride and lysophospholipid. Using shotgun proteomics, Weichhart et al identified 49 HDL-associated proteins in hemodialysis patients. [22] Compared with control, uremic HDL was enriched in surfactant protein B (SP-B), apolipoprotein C-II, SAA1, and α -1-microglobulin/bikunin precursor. In addition, the SAA levels in HDL of ESRD patients significantly correlated with impaired anti-inflammatory ability. Similar observation was made by Tolle et al who also found the HDL of dialysis patients to be enriched in SAA1 and have lower anti-inflammatory capacity. [21] Recently, Speer demonstrated that HDL of CKD patients promotes endothelial cell dysfunction, inflammation, and hypertension which the authors link to symmetric dimethylarginine. [24] Clearly, alterations in the HDL composition observed in ESRD patients may well affect a host HDL functions.

Conclusion

A potential contributor to the residual risk of CVD is HDL. Although HDL level is a recognized negative risk for CVD, the concept of HDL dysfunction provides an additional mechanism by which HDL may affect biological processes influencing CVD. Specific changes in the composition of particles within HDL as well as modifications in the proteome or lipidome of the HDL occurring in CKD may cause not only loss of its protective properties but transformation into toxic particles. Raising the levels of a dysfunctional HDL may promote damage. Therefore, therapy should be aimed at improving HDL function, possibly by targeting specific compositional moieties within the HDL particle.

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Figure 1.

Cholesterol efflux capacity and HDL-C levels showing no correlation across the range of HDL-C in ESRD patients on maintenance hemodialysis (ESRD-HD) or in normal controls.