underway (Study of Diabetic Nephropathy with Atrasentan [SONAR]). However, for ET blockers to realize their potential, further information must be obtained regarding the basic mechanisms of how and when they work. An incremental advance is the study by Lenoir et al., which demonstrates that the ET$_4$ receptor may need to be targeted as well to maximize renal protection in diabetic nephropathy. However, because of the adverse effect profile related to ET$_B$ blockade (particularly the sodium retention), basic research elucidating the mechanisms involved in ET–blockade-induced adverse effects is needed so that better strategies can be devised to correct or override them, and as a result provide a more favorable risk/benefit profile.

In summary, there is a critical need to develop additional therapies to improve the treatment of diabetic nephropathy; ET antagonists hold considerable promise. However, for this promise to be fulfilled, researchers must continue to identify the basic mechanisms by which ET-1 contributes to diabetic nephropathy, as well as the mechanisms of adverse effects induced by ET antagonists. Despite the vast volume of basic research on the ET system, the clinical trials have just emphasized the need to return to the bench to further our understanding of its fundamental mechanisms. This is important for the development of maximally effective therapeutic strategies with minimal adverse effects.

**ACKNOWLEDGMENTS**

L.A.J. is supported in part by the National Institute of General Medical Sciences of the National Institutes of Health under award number P20-GM104357 and by the John D. Bower Foundation.

**REFERENCES**


See related articles, “Direct Action of Endothelin-1 on Podocytes Promotes Diabetic Glomerulosclerosis,” and “The Endothelin Antagonist Atrasentan Lowers Residual Albuminuria in Patients with Type 2 Diabetic Nephropathy,” on pages 1050–1062 and 1073–1083, respectively.

**HDL in CKD: How Good Is the “Good Cholesterol?”**

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Published online ahead of print. Publication date available at www.jasn.org.

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In this issue of JASN, Zewinger et al. report that associations of HDL cholesterol (HDL-C) with cardiovascular and all-cause mortality are modified by eGFR. The study was performed among 3316 participants in the Ludwigsafen Risk and Cardiovascular Health study, a cohort study of patients referred for coronary angiography in Germany. Among 1209 participants with an eGFR = 90 ml/min per 1.73 m² (calculated from serum creatinine and cystatin C), baseline HDL-C ≥ 50 mg/dl was associated with a 70% lower risk of cardiovascular mortality (adjusted hazard ratio, 0.30; 95% confidence interval, 0.13 to 0.73) compared with HDL-C ≤ 25 mg/dl. By contrast, among 456 participants with an eGFR < 60, HDL-C was not associated with subsequent cardiovascular events (comparing HDL-C ≥ 50 mg/dl with HDL-C ≤ 25 mg/dl; adjusted hazard ratio, 0.82; 95% confidence interval, 0.40 to 1.69). The interaction of eGFR with HDL-C was statistically significant (P = 0.02). Zewinger et al. propose that HDL particles, which are generally thought to be atheroprotective, are rendered dysfunctional in CKD. This is an important and intriguing hypothesis that needs further experimentation.

In the general population, higher plasma concentrations of HDL-C have long been known to be associated with a reduced risk of atherosclerotic cardiovascular diseases. This association may be causal in nature. HDL plays a key role in reverse cholesterol transport, in which cholesterol is removed from macrophages in the vascular wall to HDL particles via transporters such as ATP-binding cassette transporter A1. HDL may also have additional protective functions, including moderation of inflammation and oxidative stress in the vascular wall.

However, recent studies have made it clear that raising the plasma HDL-C concentration does not necessarily reduce cardiovascular risk. For example, torcetrapib and niacin effectively raise HDL-C by reducing hepatic HDL catabolism, torcetrapib by inhibiting cholesteryl ester transfer protein (CETP), and niacin by inhibiting hepatic lipase. However, in phase 3 clinical trials, extended-release niacin did not reduce the rate of cardiovascular events when added to simvastatin and ezetimibe, and torcetrapib actually increased the risk of cardiovascular events when added to simvastatin. Nonetheless, these studies identified HDL abnormalities that may be of great importance.

With these studies, the field of HDL and cardiovascular disease has focused increasingly on HDL quality, as opposed to HDL quantity. HDL particles are complexes of lipid and protein that are formed and modified through complex interactions with the liver, vascular wall, and other lipoproteins, generally mediated by specific enzymes. The quality of these complex particles has been evaluated in three inter-related dimensions: size, composition, and function. Abundant evidence addressing these aspects of HDL quality suggests that not all “good cholesterol” is equally good.

First, epidemiologic studies suggest that large, buoyant HDL particles, subclassified as HDL₂, are most strongly associated with favorable cardiovascular outcomes. HDL₂ particles are formed from smaller, denser HDL₃ particles by the transfer of cholesterol and phospholipid from cells (by ATP-binding cassette transporter A1, such as during reverse cholesterol transport) and triglyceride-rich lipoproteins. Removal of cholesterol from HDL₂ to the liver by CETP and hepatic lipase then recycles these particles to HDL₃. By analogy, HDL is a “garbage truck” that picks up lipid debris and brings it to the liver for disposal. Under most circumstances, a high HDL₂ concentration reflects a well maintained fleet of trucks actively engaged in clean-up. However, raising HDL₂ by preventing it from dumping its greasy load (e.g., by pharmacologic inhibition of CETP or hepatic lipase) may not be beneficial and may even be harmful.

Second, HDL particles vary in their protein and lipid composition. In addition to proteins necessary for HDL to interact with the vascular wall and other lipoproteins, HDL particles contain dozens of proteins related to complement regulation, proteolysis, and the acute-phase response. Various species of free cholesterol, cholesterol esters, phospholipids, and triglycerides are also present in variable proportions. To some extent, the “cargo load” of HDL proteins and lipids may reflect what it has picked up from the vascular wall. In addition, this cargo may alter the actions of HDL.

Third, HDL particles vary in their functional capacity. Reduced HDL-mediated efflux of cholesterol from macrophages ex vivo has been associated with coronary artery disease in humans. Differences in other HDL functions, such as modulation of inflammation and oxidative stress, are less well developed.

Patients with CKD tend to have alterations in both HDL quantity and HDL quality. Even a mildly impaired GFR is associated with low HDL-C concentrations, which become progressively worse through ESRD. Moreover, with CKD, HDL tends to be smaller and denser, due in part to decreased adipose tissue lipoprotein lipase activity. In addition, Holzer et al. found significant differences in both protein and lipid composition of HDL particles isolated from 27 hemodialysis patients compared with HDL isolated from 19 normal control participants. HDL from hemodialysis patients did not remove cholesterol from macrophages ex vivo as effectively as HDL from control participants. Serum amyloid A-1, albumin, and apolipoprotein C3 in the HDL of dialysis patients negatively correlated with cholesterol efflux, suggesting that HDL composition may affect HDL function. Speer et al. found that HDL isolated from 67 patients with CKD reduced nitric oxide production from human aortic endothelial cells ex vivo, in contrast with HDL from 25 normal controls that increased nitric oxide. HDL from patients with CKD contained high levels of symmetric dimethylarginine, and the addition of symmetric dimethylarginine to HDL induced endothelial dysfunction. The studies by Holzer et al. and Speer et al. are limited by small samples of patients from single sites, comparisons with control participants who differ in terms of age, comorbidity, or medication use, and the absence of clinical outcomes. Nonetheless, these studies identified HDL abnormalities that may be of great importance.

In this context, the article by Zewinger et al. serves as a motivating study to further investigate lipoprotein
metabolism and its clinical consequences in CKD. The null association of HDL-C with cardiovascular mortality among participants with an eGFR<60 ml/min per 1.73 m² is consistent with the hypothesis that HDL particles are rendered dysfunctional in some manner in CKD. However, without data relating HDL composition or function to cardiovascular outcomes, this hypothesis remains untested. Other potential explanations for the interaction of HDL-C and eGFR include differences by eGFR in the range of HDL-C, the functional form of the association of HDL-C with mortality, confounders of the HDL-C–mortality association, the relationship of HDL-C to other lipoproteins (e.g., atherogenic small, dense LDL particles17), or the nature of the observed cardiovascular events (e.g., a greater incidence of nonatherosclerotic cardiovascular deaths that are less strongly related to lipoproteins). Moreover, although the null association of HDL-C with mortality in the Ludwigshafen Risk and Cardiovascular Health study replicated in a smaller CKD cohort, apparently conflicting results have also been reported. In the Multi-Ethnic Study of Atherosclerosis, the association of lower HDL-C with carotid intima-media thickness strengthened with a lower eGFR (as did the association of small, dense LDL with intima-media thickness).18 Dissecting the complex interplay of HDL-C, HDL size, HDL composition, and HDL function with cardiovascular disease therefore needs further investigation.

Moving research on HDL and cardiovascular disease in CKD forward will require studies that apply innovative assays of HDL quality using strong epidemiology designs. Such studies will require the following: large populations with external validation (as presented by Zewinger et al.); reliable measurements of HDL size, composition, and function; relevant measurements of vascular function in vivo or evaluation of clinical cardiovascular events; an ability to account for aspects of lipoprotein protein metabolism related to HDL (particularly differences in LDL size and density); and adequate consideration of the effects of common lipid-lowering medications, ideally further investigating the effects of these medications on HDL composition and function.

Clinically, accumulating data, including those from Zewinger et al., suggest that HDL-C should not be used as a guide to therapy in patients with CKD. Indeed, recent Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend that statins be prescribed with little regard to any circulating cholesterol concentrations, utilizing a “fire-and-forget” strategy for patients with CKD not requiring dialysis in which neither LDL cholesterol nor HDL-C is used as a major therapeutic target.19 These findings follow the design and results of the Study of Heart and Renal Protection, in which a combination of simvastatin and ezetimibe reduced the risk of atherosclerotic cardiovascular events in CKD.20 KDIGO does not advocate any specific therapies based on HDL-C, a position congruent with that of the National Lipid Association.21 HDL may become a therapeutic target in CKD, but much additional work is needed to determine whether and how that should occur.

ACKNOWLEDGMENTS

I.H.d.B. receives grant funding from the National Institutes of Health National Institute of Diabetes and Digestive and Kidney Diseases (R01-DK087726, R01-DK088762) and the National Heart, Lung, and Blood Institute (R01-HL096875).

DISCLOSURES

None.

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