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Risk factors: HDL-cholesterol levels and mortality in patients with ESRD

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**NEWS & VIEWS**

**RISK FACTORS**

**HDL-cholesterol levels and mortality in patients with ESRD**

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In the general population, risk of cardiovascular disease is inversely associated with HDL-cholesterol levels. However, a new post hoc analysis of data from the German Diabetes Dialysis study reports no correlation between HDL cholesterol and mortality among patients on dialysis—a phenomenon that the authors attribute to HDL dysfunction.


High levels of serum HDL cholesterol are generally thought to protect against cardiovascular disease. However, a recent post hoc analysis of data from 1,255 diabetic patients with end-stage renal disease (ESRD) found no significant difference in cardiovascular or overall mortality between subgroups categorized according to HDL-cholesterol levels. Silbernagel et al. attributed the lack of substantial effects of high HDL-cholesterol levels in this study to ESRD-associated HDL dysfunction. Given the proinflammatory nature of uraemic HDL, and its impaired capacity to participate in reverse cholesterol transport, the finding that high levels of dysfunctional HDL do not confer benefit in patients with ESRD is not surprising.

Chronic kidney disease (CKD) results in substantial changes to the serum concentrations of lipids and the composition and function of lipoproteins. In addition, comorbid conditions, renal replacement modalities (haemodialysis, peritoneal dialysis and renal transplantation), drug regimens and pre-existing genetic disorders of lipid metabolism modulate serum lipid and lipoprotein profiles in the CKD population. In patients on haemodialysis, levels of serum cholesterol and LDL cholesterol are generally within or below the normal limits, serum HDL-cholesterol levels are commonly reduced, and levels of serum triglycerides and VLDL are elevated. These changes are accompanied by an accumulation of highly atherogenic and proinflammatory intermediate density lipoprotein (IDL), small dense LDL, chylomicron remnants and oxidized LDL.

HDL abnormalities in patients on dialysis generally include reduced levels of serum apolipoprotein A-I (apoA-I), apolipoprotein A-II (apoA-II), HDL cholesterol and HDL phospholipids, and elevated levels of HDL-triglycerides. Maturation of cholesterol ester (CE)-poor HDL3 to CE-rich HDL2 is impaired, and HDL antioxidant, anti-inflammatory and reverse cholesterol transport properties are defective in the ESRD population. Abnormalities of HDL structure and function in advanced CKD are mediated by a reduction in the serum levels of apoA-I and apoA-II (owing to reduced biosynthesis and increased catabolism), deficiency of lecithin cholesterol acyltransferase (LCAT, which is essential for esterification of free cholesterol on the surface of HDL and the formation of CE-rich HDL), upregulation of acyl coenzyme A:cholesterol acyltransferase 1 and 2 (ACAT-1 and ACAT-2, which promote esterification and retention of intracellular cholesterol), oxidative modification of HDL, which lowers its affinity for binding to ATP-binding cassette sub-family A member 1 (ABCA1) and ATP-binding cassette sub-family G member 1, the gateways of cholesterol efflux, a reduction in the levels of the key HDL-associated antioxidant enzymes, serum paraoxonase/arylesterase 1 and glutathione peroxidase 1, and the presence of highly proinflammatory serum amyloid A protein (SAA) in the HDL of patients on haemodialysis. Hypoalbuminaemia (caused by systemic inflammation and malnutrition, which are fairly common in patients with ESRD) also contributes to reduced HDL-cholesterol levels by limiting receptor-independent transfer of albumin-bound cholesterol to HDL in the blood stream. These abnormalities work in concert to lower HDL levels and impair HDL maturation as well as its antioxidant, anti-inflammatory and reverse cholesterol transport capacities. In patients on haemodialysis, the ability of HDL to remove cholesterol from lipid-laden macrophages, reverse LDL oxidation and prevent monocyte attachment to, and infiltration of, the vascular endothelium is greatly reduced. HDL from patients with ESRD can trigger the release of inflammatory cytokines by macrophages, a phenomenon that is partly attributable to the presence of SAA.

The mechanism that underlies the elevated serum HDL cholesterol levels in a subgroup of patients with ESRD in the study by Silbernagel et al. and in other studies, is unclear. High HDL-cholesterol levels are commonly assumed to imply increased reverse cholesterol transport from peripheral tissues, but this situation is not always the case. Under normal conditions, binding of circulating discoid CE-poor HDL to ABCA1 triggers hydrolysis of intracellular CE and the release and translocation of free cholesterol to the cell membrane, where it is re-esterified by LCAT and loaded in the core of HDL. Once fully loaded, the spherical CE-rich HDL detaches and returns to the circulation. Before reaching the liver, CE-rich HDL exchanges part of its cholesterol content with the triglyceride cargo of IDL. This process, which is catalysed by cholesterol ester transfer protein (CETP), is critical for transformation of atherogenic IDL and small dense LDL to CE-rich LDL, which is readily removed by the LDL receptor in the liver, thus contributing to reverse cholesterol transport. In addition, transfer of CE to LDL enhances the capacity of HDL to remove cholesterol from peripheral tissues. On reaching the liver, CE-rich HDL unloads its lipid cargo by binding to the HDL docking receptor scavenger receptor class B member 1 (SRB1) on hepatocytes. Oxidative or myeloperoxidase (MPO) modifications of HDL (as a result of systemic inflammation and oxidative stress) can impair its ability to bind to SRB1 and unload its cholesterol cargo. In addition, oxidised or MPO-modified albumin can bind...
to SRB1 and limit HDL binding (Figure 1). Impairments of either CETP-mediated CE exchange for triglyceride with IDL and/or LDL or HDL binding to SRB1 can lead to substantial elevations of HDL cholesterol, which are associated with impaired reverse cholesterol transport and accumulation of IDL and small dense LDL particles. Such accumulation results in accelerated atherosclerosis and systemic inflammation. Thus contrary to common perception, high HDL-cholesterol levels do not necessarily suggest favourable outcomes. In fact, Honda et al. showed that patients on haemodialysis who have high HDL cholesterol concentrations have high levels of oxidized HDL and increased cardiovascular mortality. Likewise an analysis of data from 33,109 patients on chronic haemodialysis in US clinics by Moradi et al. revealed a U-shaped association between HDL cholesterol levels and all-cause and cardiovascular mortality. Patients with HDL cholesterol levels <0.78 mmol/l (30 mg/dl) or >1.55 mmol/l (60 mg/dl) exhibited significant increases in cardiovascular and all-cause mortality, whereas those with HDL cholesterol levels between 1.30 mmol/l (50 mg/dl) and 1.55 mmol/l had the highest survival.

The reasons for the differences between the results of the studies by Moradi et al., Honda et al., which showed increased mortality in patients with high HDL levels, and the study by Silbernagel et al., which showed no difference in mortality between patients in different HDL quartile subgroups, are unclear. However, several factors might account for the apparent disparities. In the latter study, all patients had diabetes mellitus, which is has a significant impact on HDL structure, function and cardiovascular complications, and 50% were treated with statins, which alters cholesterol metabolism and LDL to HDL cholesterol ratio. The highest HDL quartile was 1.47 ± 0.25 mmol/l (56.9 ± 9.6 mg/dl), which encompasses many patients with levels below the 1.55 mmol/l threshold shown to be associated with increased mortality. Moreover, the percentage of women was substantially greater, and body mass index, levels of triglycerides and C-reactive protein were lower in the highest HDL quartile than in the other quartiles. These differences might, in part, account for the high HDL levels in this subgroup. In addition, the number of patients included in the analysis by Silbernagel et al. was far smaller than the number studied by Moradi et al., which could have impacted the results of the statistical analysis. Finally differences in the ethnic backgrounds of the study populations and in environmental factors might have, in part, contributed to the apparent difference in results.

The lack of association between HDL cholesterol level and cardiovascular all-cause mortality in patients with ESRD shown by Silbernagel et al. points to HDL dysfunction, which is primarily driven by systemic inflammation and oxidative stress. Identification of the underlying mechanisms and effective treatment of systemic inflammation and oxidative stress are the key steps in restoring HDL function and lowering the burden of cardiovascular and all-cause morbidity and mortality in the ESRD population.

Figure 1 | Effects of chronic kidney disease on HDL structure and function. Scavenger-receptor-mediated internalization of ox-LDL and remnant lipoproteins by macrophages and resident cells in the artery wall leads to foam cell formation and atherosclerosis. Normal HDL mitigates these events by preventing and/or reversing the formation of ox-LDL via its constituent antioxidant enzymes, and by extracting surplus cholesterol from macrophages. The uptake of free cholesterol and its LCAT-mediated conversion to cholesterol ester results in transformation of HDL3 to HDL2. This process is generally impaired in end-stage renal disease because of LCAT deficiency. Oxidative or MPO-mediated internalization of ox-LDL and remnant lipoproteins by macrophages and resident cells in vascular and all-cause mortality, whereas

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Competing interests
The author declares no competing interests.