HDL-Mediated Cholesterol Efflux Associates with Incident Kidney Disease

To the Editor:

The functional characteristic of HDL particles to remove cholesterol from peripheral cells—cholesterol efflux capacity (CEC)—associates inversely with cardiovascular disease (CVD), independent of HDL cholesterol (HDL-C) (1). In addition to increased cardiometabolic risk, low HDL-CEC appears to be distinctive for kidney disease, including prediction of graft failure in renal transplant recipients (2). Thus, there appears to be a link between CEC and kidney function, but no previous study has looked at whether HDL-CEC was associated with incident kidney disease. The paucity of large-scale epidemiology in this area is likely owing to the complexity and cost of cellular HDL-CEC assays (1).

We analyzed HDL-CEC, 4 HDL subclass particle concentrations, standard lipoprotein lipids, apolipoprotein A-I, and creatinine by a serum nuclear magnetic resonance platform (1, 3). Two large Finnish population-based prospective cohorts were studied: DILGOM2007 (n = 4739, 47% men; median [interquartile range] for age: 54 years [42–64 years]; HDL-CEC: 20.4% [19.4%–21.8%]; and HDL-C: 1.4 mmol/L [1.2–1.7 mmol/L]) and FINRISK1997 (n = 7471, 50% men; median [interquartile range] for age: 48 years [37–59 years]; HDL-CEC: 21.8% [20.7%–23.4%]; HDL-C: 1.5 mmol/L [1.3–1.8 mmol/L]), with follow-up times of 8 and 15 years, respectively. The studies were approved by the Coordinating Ethical Committee of Helsinki and Uusimaa Hospital District, and written informed consent was obtained from all participants. The HDL-CEC values correspond to the most commonly used assay to quantify HDL-CEC, namely, the use of cAMP-treated J774 murine macrophages with radiolabeled cholesterol (1).

The HDL subclasses were defined by particle size: very large (mean diameter: 14.3 nm), large (12.1 nm), medium (10.9 nm), and small HDL (8.7 nm) (3). The association of HDL-CEC was investigated with incident kidney disease, including chronic and unspecified kidney disease (International Classification of Diseases, 10th Revision; N18–N19; Ninth Revision: 585; Eighth Revision: 58200) in comparison to other HDL-related biomarkers. Outliers for each measure were defined as values that were >4 times the interquartile range below the 25th and above the 75th percentile. For HDL-CEC, 212 outliers were detected (1.3%). To study the associations of HDL-CEC and other HDL-related measures with the incident events, participants with prevalent kidney disease (n = 16), outliers, and missing data (n = 261) were excluded before analyses, leaving complete data for 12,210 participants and 61 incident kidney disease events. Thereafter, data were analyzed by Cox proportional hazards regression models in each cohort, and the results were combined by inverse variance-weighted fixed-effects meta-analysis. Glomerular filtration rates were estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula in the R software package nephron. All statistical analyses were undertaken in R v4.0.2.

The Cox regression results for the associations of HDL-CEC and the various HDL-related concentration measures with incident kidney disease are illustrated in Fig. 1. Age- and sex-adjusted HDL-CEC was associated inversely with incident kidney disease (hazard ratio: 0.72 [95% CI, 0.57–0.92]; P = 0.009), and adjusting for traditional risk factors and HDL-C did not affect the association (hazard ratio: 0.74 [95% CI, 0.56–0.97]; P = 0.031). In contrast, none of the HDL-related concentration measures were clearly associated with incident kidney disease after corresponding adjustments (instead of HDL-C, the HDL-related concentration measures were adjusted for HDL-CEC). Adjusting for inflammation markers, C-reactive protein and glycoprotein acetyls—either alone or together—did not notably affect any association.

The current findings add to the accumulating evidence that HDL-CEC would be systemically beneficial, not only for CVD but also for the development of kidney disease. These findings also support the independent role of HDL functionality in disease risk assessment.

Large-scale epidemiological research regarding kidney disease is currently limited to HDL-C, and information on HDL-CEC and HDL subclasses are scarce. Recent Mendelian randomization analyses support a causal relationship between genetically higher HDL-C and better kidney function (4). However, genetic associations between estimated glomerular filtration rate and HDL-C are highly pleiotropic, advocating for the existence of multiple causal pathways, some of which might better relate to other HDL characteristics than cholesterol. The metabolic pathways that link HDL to glomerular microcirculation may, at least in part, be different from those for CVD. Clear-cut interpretations of the individual roles of various, both genetically and observationally correlating HDL measures, are thus challenging. It has also been demonstrated recently that the relative role of different HDL characteristics appears to depend on kidney function; the associations of HDL-CEC with CVD end points are not identical for individuals with and without kidney disease, in contrast to HDL particle concentrations (5).
Our current finding that better HDL functionality, in terms of cholesterol efflux, predicts lower incidence of kidney disease concurs well with the above-mentioned findings. Our findings advocate for continued attention to the functional attributes of HDL in the risk assessment of not only CVD but also kidney disease. Large-scale longitudinal studies would be needed to better understand the role of kidney status on these associations.

Nonstandard Abbreviations: CEC, cholesterol efflux capacity; CVD, cardiovascular disease; HDL, HDL cholesterol.

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