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Genetic and Lipoproteomic Evidence for a Non-Albuminuric Pathway to Kidney Failure Driven by LCAT Dysfunction

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Objectives : Many patients with chronic kidney disease (CKD) continue to experience a decline in renal function due to non-proteinuria pathways, even when using renin-angiotensin system blockers and SGLT2 inhibitors. We asked whether LCAT-related HDL dysfunction marks a distinct, non-albuminuric pathway to kidney failure.

Methods : We first performed two-sample Mendelian randomization using UK Biobank HDL-C instruments and CKDGen outcomes (total N=521,088). We then profiled 112 lipoprotein measures by high-resolution NMR in 1,762 biopsy-confirmed CKD patients from the KORNERSTONE cohort, derived an LCAT Phenotype Score across five prespecified domains, and tested associations with a composite outcome (ESKD or death) and ESKD using Cox models.

Results : Genetically predicted higher HDL-C was associated with lower CKD risk (IVW $\beta=-0.133$, $P=0.010$) but not with UACR ($\beta=-0.032$, $P=0.076$). In KORNERSTONE, advanced CKD showed HDL remodeling consistent with impaired esterification, including triglyceride enrichment and relative cholesteryl-ester depletion. The LCAT Phenotype Score tracked with lower eGFR ($r=-0.28$, $P<0.001$) and was unrelated to albuminuria ($r=-0.01$, $P=0.68$). Over 3.1 years median follow-up, each 1-SD increase predicted the composite outcome after full adjustment including UACR (HR 1.21, 95% CI 1.09–1.34) and showed no interaction with albuminuria.

Conclusions : An LCAT-linked lipoproteomic phenotype identifies CKD risk that is largely orthogonal to albuminuria and concentrates in near-term events, supporting a metabolically defined pathway to kidney failure that may enable precision stratification.

图片 1.jpg

