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Ectopic accumulations of cholesteryl esters containing increased polyunsaturated fatty acids contribute to age-dependent lipotoxicity in the kidney

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Objectives: Ectopic lipid accumulations in the kidney contribute to oxidative stress and cellular injury, a process termed lipotoxicity. However, the impacts of aging on renal lipotoxicity are largely unknown. Here, we investigated the age-dependent alterations in renal lipid profiles and metabolisms, pathogenesis of lipid accumulations, and their biological consequences.

Methods: Two-, 12-, and 24-month-old male mice were used to compare renal phenotypes as well as renal lipidomics. We further evaluated molecular characteristics of intrarenal lipid depositions and changes in oxidative stress with aging.

Results: Twenty-four-month-old mice showed evidences of kidney fibrosis and oil red O-positive cytoplasmic vacuoles in renal tubular cells. Age-dependent accumulation of cholesteryl esters containing increased polyunsaturated fatty acids was common lipid abnormalities in glomeruli, tubules, and platelet-derived growth factor receptor-β-positive interstitial cells, but not in plasma. Transcriptomic profiles associated with lipid metabolism were not significantly altered with age, while aberrant autophagic activities were observed in kidneys of 24-month-old mice. Renal tubular vacuoles in 24-month-old mice contained heterogeneous inner materials and expressed both BODIPY and LC3, indicating that these organelles were lipid-laden atypical autophagosomes. Consistently, isolates of lipid droplets were enriched with cholesteryl esters with polyunsaturated fatty acid and co-expressed LC3. Finally, lipid peroxidation was increased in kidneys of 24-month-old mice and mainly occurred along the margins of lipid-laden atypical autophagosomes.

Conclusions: Renal aging is characterized by abnormal accumulations of cholesteryl esters bound to polyunsaturated fatty acid, as forms of lipid-laden atypical autophagosomes in tubular epithelial cells, and these ectopic intracellular lipids are associated with age-dependent increases in oxidative stress.