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Beyond Challenges, Towards Healthier Kidney

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Impact of Fatty Acid Desaturase 1 (FADS1) on Chronic Kidney Disease via Very-Low-Density Lipoprotein-Associated Metabolites: A Drug Target Mediation Mendelian Randomization Study

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Objectives : Metabolic dysregulation plays a crucial role in chronic kidney disease (CKD). Identifying new targets for CKD through metabolites and their regulatory genes requires further investigation.
Methods : A total of 233 metabolites from the GWAS Catalog were utilized for Mendelian randomization with chronic kidney disease (CKD). External validation was conducted using data from the UK Biobank. Cis-expression quantitative trait loci (cis-eQTLs) of genes related to very-low-density lipoprotein (VLDL) were selected for Mendelian randomization with CKD and metabolites. The total effect of fatty acid desaturase 1 (FADS1) on CKD and metabolite-mediated effects were calculated using the two-step Mendelian randomization method. Bulk RNA sequencing was used to validate FADS1 overexpression in the kidney tissues of patients with CKD. Correlation analysis was conducted to explore the relationship between FADS1 and common clinical indicators.
Results : The cholesteryl esters to total lipids ratio in medium VLDL (odds ratio [OR] = 0.84 [0.77–0.92]; P.adj = 0.039) and total cholesterol to total lipids ratio in small VLDL (OR = 0.84 [0.77–0.91]; P.adj = 0.003) were protective factors for CKD, whereas the triglycerides to total lipids ratio in small VLDL (OR = 1.18 [1.09–1.27]; P.adj = 0.009) and the triglycerides to total lipids in very small VLDL (OR = 1.19 [1.10–1.27]; P.adj < 0.001) were risk factors. They mediated the risk of CKD by FADS1 (OR = 1.11 [1.06–1.17]; P.adj = 0.001), and mediation effects of 21.17%, 10.43%, 23.52%, and 29.96% were found. The differential expression of FADS1 was observed in the kidney tissues of patients with CKD. Overexpression of FADS1 is associated with higher blood pressure, elevated creatinine levels, and reduced glomerular filtration rate.
Conclusions : FADS1 is a risk factor for CKD and a novel therapeutic target. VLDL-associated metabolites may mediate the detrimental effect of FADS1 in CKD.

Graphical abstract.jpeg

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