



Beyond Liver Disease: Non-Alcoholic Fatty Liver Disease and Advanced Liver Fibrosis in Kidney Disease

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Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease; globally, a quarter of the general population is affected [1]. In recent decades, the increasing prevalence of NAFLD has been linked to the alarming increase in obesity, insulin resistance, and type 2 diabetes mellitus (T2DM), which are risk factors for both NAFLD and chronic kidney disease (CKD). The main etiologies of chronic liver disease in Korea have shown a decreasing trend of hepatitis B infection and an increasing trend of NAFLD [2,3]. NAFLD comprises a broad spectrum of liver diseases ranging from simple steatosis (non-alcoholic fatty liver [NAFL]) and non-alcoholic steatohepatitis (NASH) to liver fibrosis and liver cirrhosis. Unlike NAFL, which has a relatively favorable outcome when unaccompanied by metabolic impairment, NASH involves hepatocyte injury and inflammation; therefore, NASH is regarded as an early stage in the progression to hepatic fibrosis or cirrhosis [4].

Among multiple organs affected by NAFLD, the kidney is the major counterpart which shares denominator underlying metabolic impairments with liver disease. NAFLD involves a scope of kidney dysfunctions from albuminuria to CKD. The epidemiological evidence suggests that NAFLD is an independent risk factor for albuminuria, and the severity of steatosis is correlated with albuminuria prevalence [5,6]. Moreover, advanced liver fibrosis is associated with proteinuria and increased urinary markers regardless of albuminuria presence [7,8]. In the literature, several cross-sectional studies found that the prevalence of CKD (defined as estimated glomerular

filtration rate [eGFR] less than 60 mL/min/1.73 m²) was much greater in patients with biopsy-proven NAFLD/NASH than in those without NAFLD or NASH [9,10]. Although these findings were consistent after adjusting confounding factors, it is still difficult to distinguish a clear causal relationship between NAFLD and CKD when those diseases co-exist and share common risk factors. Additionally, the original definition of CKD, abnormalities in kidney function or structure that persist over 3 months, is hard to confirm in cross-sectional design. Few longitudinal studies on NAFLD and incident CKD have been conducted, especially in a population with T2DM.

In this issue of the *Diabetes and Metabolism Journal*, Seo et al. [11] demonstrated a causal relationship of NAFLD assessed by ultrasound and advanced liver fibrosis in CKD incidence in a longitudinal cohort study. Over a mean follow-up period of 8.3 years, patients with advanced liver fibrosis had a higher risk of incident of CKD compared to those without advanced liver fibrosis (hazard ratio, 1.59 to 1.75; all $P < 0.05$). Interestingly, an increased CKD incidence was not observed when dividing by NAFLD presence. This finding was similar the results of Jang et al. [12], who showed that the severity of NAFLD was associated with a decline in annual eGFR change, and an annual eGFR change in NAFLD was not observed in subgroup analysis in patients with T2DM. Another Korean study demonstrated that the increased incidence of CKD in NAFLD did not indicate a direct association between NAFLD and CKD in diabetes subgroup analysis [13]. Compared to previous Italian longitudinal studies of NAFLD in populations with diabetes,

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which concluded that NAFLD increased the risk of incident CKD [14,15], the current study population had a relatively short duration of diabetes (mean duration of diabetes 7.4 years vs. 11 to 18 years in Italian studies). Of note, Asian patients with diabetes are more susceptible to kidney complications than their Caucasian counterparts [16]. As the authors stated, the longer follow-up duration of the current study (8.3 years vs. 5.2 to 6.5 years in Italian studies) might have influenced the discrepancy.

The longitudinal study by Seo et al. [11] provided additional information supporting that T2DM patients with severe forms of NAFLD are more likely to progress to CKD, which is a strong predictor for cardiovascular events and overall mortality. This study has contributed to our understanding of NAFLD in Asian populations with diabetes. Although further investigations are needed to determine the direct effect of NAFLD on CKD, and on crosstalk between the liver and kidneys, it is important for healthcare providers to consider NAFLD as a potential indicator for high risk of CKD. Comprehensive approaches including NAFLD assessment are needed to manage patients with diabetes.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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