Letter

Diabetes Metab J 2022;46:953-955
https://doi.org/10.4093/dmj.2022.0374
pISSN 2233-6079 · eISSN 2233-6087

dmj
DIABETES & METABOLISM JOURNAL

Advanced Liver Fibrosis Is Associated with Chronic Kidney Disease in Patients with Type 2 Diabetes Mellitus and Nonalcoholic Fatty Liver Disease (*Diabetes Metab J* 2022;46:630-9)

Ji Hye Huh

Department of Internal Medicine, Hallym University College of Medicine, Chuncheon, Korea

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease worldwide. In patients with type 2 diabetes mellitus (T2DM), the prevalence of NAFLD is up to 70%. Although hepatic damage is a known cause of NAFLD, the clinical burden of NAFLD is also due to extra-hepatic organ diseases, including chronic kidney disease (CKD). Moreover, NAFLD with advanced fibrosis is considered a more severe form of NAFLD associated with an increased risk of liver-related mortality and extra-hepatic disease compared with NAFLD with simple steatosis and low fibrosis stage. Although several studies have shown the relationship between liver fibrosis score and incident CKD in individuals without diabetes, this relationship in patients with T2DM is not well established.

In this article entitled "Advanced liver fibrosis is associated with chronic kidney disease in patients with type 2 diabetes mellitus and nonalcoholic fatty liver disease," Seo et al. [1]. report the association between the presence and severity of NAFLD and incident CKD in patients with T2DM. In the longitudinal cohort study of patients with T2DM, the results showed that CKD developed in 220 (15.1%) patients in the non-NAFLD group, in 231 (14.1%) patients in the NAFLD without advanced fibrosis group, and in 28 (31.1%) patients in the NAFLD with advanced fibrosis group. No increased risk of incident CKD in the NAFLD group was observed compared to the non-NAFLD group (P=0.435). However, among patients with NAFLD, advanced liver fibrosis was associated with an increased risk of CKD (adjusted hazard ratio, 1.75; 95% confidence interval, 1.15 to 2.66; P=0.009). These findings are consistent with previous reports that have shown an association between high liver fibrosis score and diabetic kidney disease [2].

Considering the well-known common pathogenesis of liver fibrosis and kidney disease deriving from the toxic effects of excess lipids, the hypothesis is reasonable. However, there are several issues to be discussed. First, as noted by the author, this study used fibrosis prediction models instead of histological confirmation to measure advanced liver fibrosis. Advanced liver fibrosis, measured by the fibrosis-4 (FIB-4) index, might not be causal and may simply be correlated with the onset of CKD. Based on the formula=age (year)×AST (IU/L)/[√ALT (IU/L)×platelet count (10^9/L)], the FIB-4 index can increase due to aging and an increase in aspartate aminotransferase (AST) to alanine aminotransferase (ALT) ratio or by a decrease in platelet count. Therefore, FIB-4 or NAFLD fibrosis scores are generally recommended for screening high-risk patients. Recently, the Fatty Liver Research Group of the Korean Diabetes Association stated that using these scores in conjunction with imaging studies is a reasonable approach [3]. Moreover, determination of a causal association between advanced liver fibrosis and incident CKD may not be possible, given the observational na-

Corresponding author: Ji Hye Huh https://orcid.org/0000-0001-5445-8007
Department of Internal Medicine, Hallym University College of Medicine,
1 Hallimdaehak-gil, Chuncheon 24252, Korea
E-mail: jihyeheo02@gmail.com

ture of this study. For this reason, further large-scale prospective studies using other advanced imaging techniques for assessing advanced liver fibrosis, such as magnetic resonance or transient elastography, in addition to biomarkers, are needed to determine the causal relationship between advanced-stage NAFLD and CKD.

Second, specific anti-diabetic medications used by study participants should be considered in the final analysis. Through recent clinical studies, several specific anti-diabetic medications, including sodium-glucose cotransporter 2 inhibitors (SGLT2i) or glucagon-like peptide-1 receptor agonist (GLP-1RA), have shown beneficial effects on renal outcomes independent of glycemic control status [4-7]. In addition, a recent meta-analysis demonstrated that SGLT2i and GLP-1RA might improve liver enzymes and hepatic steatosis. This should encourage further research into the possible utility of these drugs in treating NAFLD [8]. Collectively, SGLT2i and GLP-1RA may independently influence liver enzymes as well as kidney and renal outcomes and might act as a confounding factor in the association between liver fibrosis score and kidney function. However, the authors did not show data on the use of these medications among study participants and did not adjust the use of SGLT2i and GLP-1RA in multivariable regression analyses. Providing information about the use of these medications in the current study population would be helpful.

Last, most variables in the non-NAFLD and NAFLD groups had *P* values of less than 0.05, indicating significant differences between the subgroups. A causal relationship between NAFLD and CKD is difficult to prove given the many shared risk factors, including insulin resistance, hyperglycemia, hypertension, dyslipidemia, and obesity. Therefore, significant differences were identified in most of the variables at baseline among the NAFLD subgroups. Although the authors showed a significant association between advanced liver fibrosis and incident CKD after adjustment for some variables, stratified analyses based on categories of known common risk factors could provide more information. In addition, to determine the independent association between NAFLD and CKD, a propensity score matching approach could be used to balance baseline covariates between the subgroups. Moreover, the authors did not provide information on lifestyle patterns such as diet, physical activity, smoking status, and/or alcohol consumption. Lifestyle patterns are important risk factors for NAFLD and CKD; they also independently contribute to clinical outcomes; therefore, appropriate adjustments are needed for the analysis.

This topic raises some discussion points about the potential role of therapeutic options for metabolic dysfunction-associated liver fibrosis in preventing CKD in patients with T2DM. Although preventative strategies for CKD in NAFLD are limited, treatment directed specifically for nonalcoholic steatohepatitis (NASH) in the future will hopefully ameliorate renal dysfunction progression in affected patients. Currently, there are no U.S. Food and Drug Administration (FDA) approved treatments for advanced liver fibrosis. However, many drugs are being developed for treating NASH, including incretin-based therapies, farnesoid X receptor (FXR) agonists, and pan- peroxisome proliferator-activated receptors (PPARs) agonists [3]. If these drugs show safety and efficacy in improving NASH, they may improve renal function in patients with T2DM. Aside from drugs, other measures to delay liver fibrosis progression may also help preserve kidney function in patients with T2DM. Although several studies, including the current one, have only found the relationship between advanced liver fibrosis and CKD, the findings of these studies should be used in managing patients with T2DM in clinical practice.

CONFLICTS OF INTEREST

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

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