

# 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)

Da Hea Seo, So Hun Kim

Division of Endocrinology and Metabolism, Department of Internal Medicine, Inha University College of Medicine, Incheon, Korea


We appreciate your interest in and comments on our article entitled “Advanced liver fibrosis is associated with chronic kidney disease in patients with type 2 diabetes mellitus and nonalcoholic fatty liver disease” that was published in *Diabetes & Metabolism Journal* [1]. You pointed out the limitations of using non-invasive biomarker models to diagnose advanced fibrosis. You also mentioned potential renal protective effects of specific anti-diabetic medications, such as sodium-glucose co-transporter 2 inhibitors (SGLT2i) or glucagon-like peptide-1 receptor agonist (GLP-1RA), as well as lifestyle patterns.

As mentioned in our manuscript, we did not perform a liver biopsy to diagnosis nonalcoholic fatty liver disease (NAFLD) or advanced fibrosis. Instead, we used validated non-invasive biomarker models such as fibrosis-4 (FIB-4) or the NAFLD fibrosis score (NFS), as well as abdominal ultrasonography for large-scale screening [2,3]. Most published studies have also used these methods, therefore, our results are comparable to previously published studies. Moreover, the 5.4% prevalence rate of  $\geq$ F3 (advanced fibrosis) in individuals with DM in this study is in agreement with reports using liver biopsy (~5%) [4,5] or magnetic resonance elastography (7%) [6].

We agree that a causal association between advanced liver fibrosis and incident chronic kidney disease (CKD) cannot be confirmed due to the observational design of this study. However, data from a clinical trial involving 261 patients with

NAFLD showed that improvement in liver histology due to lifestyle modifications such as weight loss were linked with significantly improved renal outcomes [7], strongly suggesting the causal relationship between severity of NAFLD and CKD. Moreover, in a recent Chinese prospective trial in elderly type 2 diabetes mellitus (T2DM) patients, where they assessed advanced liver fibrosis with FIB-4 and NFS, there was a significant association between NAFLD fibrosis and CKD occurrence and progression, of which results were comparable to our study [8].

As for the potential renal protective effect of specific anti-diabetic medications, such as SGLT2i or GLP-1RA, this study enrolled patients from January 2000 to December 2016, when the annual prescription rate of both SGLT2 inhibitors and GLP-1 agonists were rather low [9] and neither SGLT2i nor GLP-1RA were prescribed to our study participants. As far as the differences in baseline covariates between the subgroups, it would have been nice if we used a propensity score matching (PSM) to balance data to approximate complete randomization, however given the small sample size in the NAFLD without fibrosis group, PSM may leave too few cases for meaningful analysis. In regard to lifestyle patterns, we have excluded those with significant alcohol consumption. Moreover, when we adjusted for current smoking and regular exercise (3 times/week), the results remained similar to Table 4, although the

Corresponding author: So Hun Kim  <https://orcid.org/0000-0002-2554-3664>  
Division of Endocrinology and Metabolism, Department of Internal Medicine, Inha University College of Medicine, 27 Inhang-ro, Jung-gu, Incheon 22332, Korea  
E-mail: shoney@inha.ac.kr

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proportions of current smokers and regular exercisers at baseline were significantly different among the groups. However, this does not reflect temporal changes in their lifestyle patterns, which may have more impact on the development of incident CKD. Lastly, we did not collect any information on diet. Future prospective trials are warranted to examine the effects of different anti-diabetic medications and lifestyle patterns on hepatic and renal outcomes in patients with T2DM. Nevertheless, our study has clearly demonstrated that advanced liver fibrosis in patients with NAFLD is independently associated with an increased risk of incident CKD in patients with T2DM.

### CONFLICTS OF INTEREST

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

### REFERENCES

1. Seo DH, Suh YJ, Cho Y, Ahn SH, Seo S, Hong S, et al. 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.
2. Huh JH, Kim JY, Choi E, Kim JS, Chang Y, Sung KC. The fatty liver index as a predictor of incident chronic kidney disease in a 10-year prospective cohort study. *PLoS One* 2017;12:e0180951.
3. McPherson S, Stewart SF, Henderson E, Burt AD, Day CP. Simple non-invasive fibrosis scoring systems can reliably exclude advanced fibrosis in patients with non-alcoholic fatty liver disease. *Gut* 2010;59:1265-9.
4. Younossi ZM, Golabi P, de Avila L, Paik JM, Srishord M, Fukui N, et al. The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: a systematic review and meta-analysis. *J Hepatol* 2019;71:793-801.
5. Kwok R, Choi KC, Wong GL, Zhang Y, Chan HL, Luk AO, et al. Screening diabetic patients for non-alcoholic fatty liver disease with controlled attenuation parameter and liver stiffness measurements: a prospective cohort study. *Gut* 2016;65:1359-68.
6. Doycheva I, Cui J, Nguyen P, Costa EA, Hooker J, Hofflich H, et al. Non-invasive screening of diabetics in primary care for NAFLD and advanced fibrosis by MRI and MRE. *Aliment Pharmacol Ther* 2016;43:83-95.
7. Vilar-Gomez E, Calzadilla-Bertot L, Friedman SL, Gra-Oramas B, Gonzalez-Fabian L, Villa-Jimenez O, et al. Improvement in liver histology due to lifestyle modification is independently associated with improved kidney function in patients with non-alcoholic steatohepatitis. *Aliment Pharmacol Ther* 2017;45:332-44.
8. Sun Y, Hong L, Huang Z, Wang L, Xiong Y, Zong S, et al. Fibrosis risk in nonalcoholic fatty liver disease is related to chronic kidney disease in older type 2 diabetes patients. *J Clin Endocrinol Metab* 2022;107:e3661-9.
9. Lee KA, Jin HY, Kim YJ, Im YJ, Kim EY, Park TS. Treatment patterns of type 2 diabetes assessed using a common data model based on electronic health records of 2000-2019. *J Korean Med Sci* 2021;36:e230.