In Response:

We appreciate Dr. Khalid and colleagues' interest in our study (1). We acknowledge the limitations highlighted by them, underscoring the inherent challenges in using ultrasound and non-invasive methods for accurate fatty liver and fibrosis assessment. Due to the retrospective design of our study, incorporating other, more accurate non-invasive methods, such as quantitative ultrasound with computer-assisted hepatic/renal ratios, hepatic attenuation rate, or magnetic resonance imaging derived proton-density-fat-fraction, was not feasible, necessitating further research with robust diagnostic tools.

For fibrosis assessment, we employed specific cutoff values for the fibrosis-4 (FIB-4) index to categorize individuals into low (FIB-4 <1.30), intermediate (FIB-4 1.30-2.67), and high (FIB-4 ≥2.67) probability of advanced fibrosis, as previously applied (2). The threshold for high probability of advanced fibrosis coincides with the cutoff value of 2.68 suggested by Roh et al. (3). Unfortunately, due to a limited number of high probability cases, we combined intermediate/high scores to analyze nonalcoholic fatty liver disease (NAFLD) severity's dose-response with incident diabetes, influenced by our relatively healthy and youthful participants. To validate findings, research among higher-risk cohorts is crucial.

Frequently sampled intravenous glucose tolerance test offers robust correlation with hyperinsulinemic euglycemic clamp compared to homeostasis model assessment of insulin resistance, yet its applicability is constrained by invasive nature, requiring IV administration of glucose and insulin, along with multiple blood draws over time, and impracticality for routine health examinations (4).

In relation to the potential role of hepatocellular (HCC) and its metastasis in type 2 diabetes mellitus (T2DM) development, as suggested by Dr. Khalid et al., hyperglycemia in T2DM, can both promote cancer cell growth and be a complication associated with the spread of metastatic tumors (5). However, we excluded individuals with a history or diagnosis of cancer (including 95 cases of HCC) or other liver-related comorbidities from our initial study population. During the follow-up period, a total of 44 incident cases of HCC (0.02%) were identified based on self-reported physician diagnoses. Given the relatively limited number of HCC cases identified, the occurrence of these cases would not have significantly impacted our primary analysis. Further research is essential to comprehend HCC's impact on NAFLD-related T2DM.

References

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