A Simple Test to Identify the Risk of NASH and Cirrhosis in People With Obesity or Diabetes: The Time to Screen Is Now

Kenneth Cusi

Division of Endocrinology, Diabetes and Metabolism, University of Florida, Gainesville, FL, USA

Correspondence: Kenneth Cusi, MD, Division of Endocrinology, Diabetes and Metabolism, University of Florida, 1600 SW Archer Rd, Rm H-2, Gainesville, FL 32610, USA. Email: Kenneth.Cusi@medicine.ufl.edu.

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The term “nonalcoholic fatty liver disease” involves a broad spectrum of disease, ranging from hepatic steatosis (only) to nonalcoholic steatohepatitis (NASH) and cirrhosis, in the absence of ongoing or recent consumption of significant amounts of alcohol or the presence of secondary causes of fatty liver disease. It is also associated with an increased risk of hepatocellular carcinoma. The condition is more common in certain high-risk groups, such as those with insulin resistance and metabolic syndrome, prediabetes, or type 2 diabetes mellitus (T2DM) or in the presence of elevated plasma aminotransferases or steatosis on imaging (1-4). Early screening and risk stratification for advanced liver fibrosis in such groups is critical in primary care and endocrinology clinics to prevent future cirrhosis. While the best screening approach remains unclear, most noncommercial panels using a combination of clinical features [age, body mass index (BMI), presence of diabetes] with routine chemistries [ie, fibrosis-4 index (FIB-4), nonalcoholic fatty liver disease fibrosis score (NFS), aspartate aminotransferase (AST) to platelet ratio index (APRI), BARD] are inexpensive, simple, and have a good negative predictive value (NPV) to rule out advanced liver fibrosis or cirrhosis. While historically FIB-4 and NFS have been the 2 most broadly tested, recent consensus statements (1-3) recommend risk stratifying for clinically significant fibrosis (>F2) in primary care and endocrinology clinics with the FIB-4 index. This index calculates the risk of hepatic fibrosis from the computation of age, plasma aminotransferases [AST and alanine aminotransferase (ALT)], and platelet count. While it has some similar limitations of other diagnostic panels such as NFS, APRI, and BARD [in particular, modest positive predictive value (PPV)] and an indeterminate zone between its low and high probability of disease, recent studies provide robust evidence that FIB-4 predicts future liver outcomes, such as cirrhosis and even of hepatocellular carcinoma (1-3). In contrast, the NFS is considered to misclassify more the prevalence of hepatic fibrosis in people with obesity and T2DM (5, 6). The performance of FIB-4 may be improved in patients with T2DM by using a higher cutoff (>1.67 vs >1.3) that reduces the indeterminate zone by about half, decreasing the need for specialist referral (5). However, larger validation studies are needed. The challenge remains on whether these inexpensive panels can be optimized (ie, NFS) for fibrosis risk stratification and which is the best test to follow an initial FIB-4 testing. A recent study by Qadri et al (7) is a welcome work toward answering these questions. Aiming to evaluate biomarker performance for advanced liver fibrosis in obese individuals, the investigators tested in a large cross-sectional cohort study (n = 1237) simple panels [FIB-4, NFS, APRI, BARD, Hepamet fibrosis score (HFS)] and newer proprietary scores that combined neo-epitope biomarkers PRO-C3 (ADAPT, FIBC3) or CK-18 (MACK-3) with use of metabolic or clinical variables. They recruited from endocrinology clinics patients planning to undergo bariatric surgery (liver biopsy done intraoperatively) and ~20% from hepatology settings (overall median BMI 40.3 kg/m²). Additionally, to derive BMI-adjusted cutoffs for NFS, they added 2 cohorts of less obese patients from hepatology clinics (all having percutaneous liver biopsies). Biomarker performance was tested by standard methods (ie, area under the receiver operating characteristic, sensitivity, specificity, and predictive values) to identify histological stage ≥F3 fibrosis or NASH with ≥F2 fibrosis (fibrotic NASH). Their main results supported the use of the simple FIB-4 index as the best way to identify ≥F2 or ≥F3 fibrosis, together with PRO-C3–based testing (ADAPT, FIBC3) and HFS. For fibrotic NASH, the best predictors were also ADAPT and FIB-4, although CK-18/MACK-3 also performed well. Of interest, sequentially combining FIB-4 with PRO-C3–based testing (ADAPT or FIBC3) increased the specificity to diagnose advanced fibrosis (≥F3). In contrast, the specificities of NFS, BARD, and FIBC3 (that include BMI in their calculation) deteriorated as a function of worsening obesity. The authors concluded that in obese patients, the best-performing fibrosis biomarkers were the inexpensive FIB-4 and PRO-C3–based testing, which are unaffected by BMI. The study is of significant value as it recruited a large cohort of patients with liver histology and compared
head-to-head commonly used noncommercial with proprietary biomarker panels, examining their use alone and in sequence. Recent guidelines recommend as a first step the use of FIB-4 and as a second step transient elastography or commercial biomarkers, if imaging is not available. In this regard, PRO-C3-based testing emerges as a very valid option. A smaller single-center study had envisioned the use of PRO-C3 to this end and how the sequential use of FIB-4 and PRO-C3 could reduce the number of liver biopsies in patients with overweight/obesity and T2DM (8). In addition, while CK-18, either as a marker of total cell death (M65) or of apoptosis (M30), had a modest performance to identify advanced fibrosis alone, it performed well for the diagnosis of NASH with advanced fibrosis (fibrotic NASH). However, adding a measurement of insulin resistance (homeostasis model assessment) and AST to CK-18 (in the MACK-3) had no major impact on their performance.

Another important aspect of the study was the intense evaluation of how obesity negatively impacts the performance of NFS. Having BMI embedded in the NFS calculation appears to be the obvious reason. The investigators derive/validate new cutoffs for NFS to rule in/out the 3 cohorts (as they had different proportions of patients with obesity and diabetes), stratify all biomarkers by the presence of diabetes (where biomarkers seem to perform worse), and validate their performance in new cohorts from the real-world setting of primary care and endocrinology clinics. Moreover, comparisons with transient elastography and other proprietary biomarkers (ELF, NIS4, among others) may expand our use of these tests.

In summary, more studies of this nature are needed to further improve our screening strategies. The central message for the endocrinologist is that this study confirms that the time for screening is now. More patient and clinician awareness are needed. Today, a simple test such as FIB-4 that can be embedded within our electronic medical records (ie, we have incorporated it at the University of Florida, together with a clinical care pathway to refer to hepatology) can efficiently screen and risk-stratify patients and prevent future cirrhosis in many people with obesity or T2DM—within seconds.

**Data Availability**

Data sharing is not applicable to this article as no data sets were generated or analyzed during the current study.

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