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Editorial

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Screening for advanced liver fibrosis in overweight and obese patients with NAFLD

Norbert Stefan[1,2,3]

[1]Department of Internal Medicine IV, Division of Endocrinology, Diabetology and Nephrology, University Hospital of Tübingen, Tübingen 72076, Germany.
[2]Institute of Diabetes Research and Metabolic Diseases (IDM) of the Helmholtz Center Munich, Tübingen 72076, Germany.
[3]German Center for Diabetes Research (DZD), Neuherberg 85764, Germany.

Correspondence to: Prof. Norbert Stefan, Department of Internal Medicine IV, Division of Endocrinology, Diabetology and Nephrology, University Hospital of Tübingen, Tübingen 72076, Germany. E-mail: norbert.stefan@med.uni-tuebingen.de

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Globally, cirrhosis is the leading cause of liver-related mortality[1]. Deaths due to cirrhosis accounted for 2.4% of total deaths globally in 2017 compared with 1.9% in 1990. Furthermore, cirrhosis caused by non-alcoholic steatohepatitis (NASH) steadily increased, while most other causes of cirrhosis decreased[2]. Thus, soon NASH may overtake viral hepatitis as the main cause of cirrhosis. As NASH is difficult to diagnose, requires liver biopsy in most cases, and develops from non-alcoholic fatty liver (NAFL), the focus on non-alcoholic fatty liver disease (NAFLD), including NAFL and NASH[3], is of major clinical and scientific interest in the pathogenesis of cirrhosis. However, the natural history of NAFLD is heterogeneous. Several main mechanisms are considered to be involved in its pathogenesis, including liver-related genetic risk, increased hepatic *de-novo* lipogenesis, gut dysbiosis and inflammation and increase of adipose tissue in the visceral compartment which is associated with increased release of fatty acids and cytokines and dysregulated release of adipokines[4-10].

NAFLD is an important risk factor for hepatocellular carcinoma[11], type 2 diabetes[12] and cardiovascular disease[13] and represents an important cause and complication of liver transplantation[14]. Although patients with NAFL can develop NASH and progressive fibrosis, which puts them at an increased risk of morbidity

and mortality, only fibrosis, but no other histological liver characteristics, was shown to independently predict increased all-cause and disease-specific mortality in patients with NAFLD[15-17]. Furthermore, among the different stages of fibrosis, fibrosis stages F3 and F4 were particularly associated with increased risks of liver-related complications and death[18].

Liver biopsy is the gold standard for the assessment of liver fibrosis[19]. However, it has several limitations such as sampling error and complications due to its invasive nature[20]. Therefore, there is a large interest in identifying noninvasive methods and tests to estimate liver fibrosis. Among them are blood-based markers, clinical scores and imaging-based markers of liver fibrosis[21,22]. While most of the blood-based markers and clinical scores of fibrosis are widely available and, in most cases, relatively cheap, the imaging-based markers of fibrosis are quite expensive. Kanwal and colleagues' call to action[23], and the associated clinical care pathway[24], suggested a global guiding strategy to promote the early diagnosis of NAFLD and NASH, starting in the primary care clinic. Three high-risk groups of people were identified by the task force: people with diabetes, those with metabolic syndrome, and people with steatosis or increased concentrations of plasma aminotransferases (ALT and/or AST), or both[24]. Furthermore, the Fibrosis-4 (FIB-4) index was selected as the initial screening tool. This pathway is intended to be used in settings where care for patients with NAFLD is provided, including primary care, endocrine, obesity medicine, and gastroenterology practices.

Following up on these recommendations derived from experts' opinions, Bril, Cusi and colleagues now undertook an important study evaluating the performance of different strategies to select patients at high risk of advanced liver fibrosis (F3 and F4) among overweight and obese subjects[25]. For this purpose, they analyzed data from a total of 275 overweight and obese patients who were recruited from hepatology and endocrinology clinics at the University of Florida in Gainesville, FL and the University of Texas Health Science Center at San Antonio (UTHSCSA) in San Antonio, TX, as well as from the general population. When NAFLD was diagnosed, patients had a percutaneous liver biopsy. The authors identified 29 patients with advanced fibrosis. Five selection strategies were compared to determine the best screening algorithm: (1) a "metabolic approach": selecting patients based on HOMA-IR ≥ 3; (2) a "diabetes approach": selecting only patients with type 2 diabetes; (3) an "imaging approach": selecting patients with hepatic steatosis based on ^{1}H-magnetic resonance spectroscopy (MRS); (4) a "liver biochemistry approach": selecting patients with elevated ALT (i.e., ≥ 30 IU/L for males and ≥ 19 IU/L for females); and (5) universal screening of all overweight and obese patients. FIB-4 index, NAFLD fibrosis score (NFS), and APRI (AST-to-platelet ratio index) were applied as screening strategies. Three important findings were derived from this study. First, among the noninvasive tests in a universal screening approach, the best performance had APRI, with 24 patients from 100 requiring a liver biopsy and a number of biopsies per patient identified with advanced fibrosis of 3.05. Second, universal screening in overweight and obese subjects, even with the APRI, is not justified as it would result in a higher number of false positive results compared to more restrictive strategies. Among the best strategic approaches in overweight and obese subjects were the application of APRI in patients with elevated ALT levels (24 patients from 100 requiring a liver biopsy and a number of biopsies per patient identified with advanced fibrosis of 2.95) and in patients with NAFLD diagnosed by ^{1}H-MRS (23 patients from 100 requiring a liver biopsy and a number of biopsies per patient identified with advanced fibrosis of 2.81). Third, pre-selection of patients based on the diagnosis of diabetes or elevated HOMA-IR followed by APRI resulted in the lowest numbers of patients requiring a biopsy (16 and 18 per 100 and 2.26 and 2.50 biopsies of patients identified with advanced fibrosis). However, the sensitivities of these strategies were lower (66% and 69% *vs.* 76% and 76%) than pre-selection based on elevated ALT levels or NAFLD diagnosed by ^{1}H-MRS.

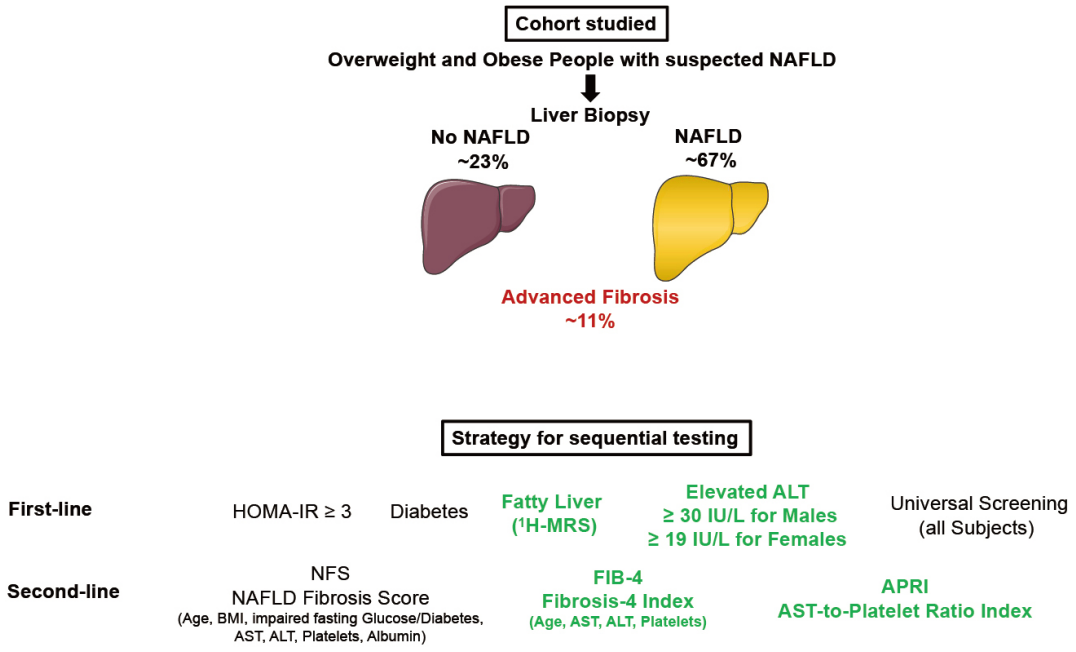

Figure 1. Cohort studied and methods used for sequential screening for advanced fibrosis. NAFLD: Non-alcoholic fatty liver disease; ^{1}H-MRS: ^{1}H-magnetic resonance spectroscopy; NFS: NAFLD fibrosis score.

With their present work, Bril, Cusi and colleagues follow up on their important studies[26-28] showing that the prevalence of 20% of moderate-to-advanced fibrosis in patients with type 2 diabetes is twice as high as in patients with steatosis but without diabetes. Furthermore, they found that one in six patients with type 2 diabetes and unknown NAFLD had moderate-to-advanced fibrosis. In addition, they showed that imaging, e.g., transient elastography, and diagnostic panels, e.g., FIB-4 index and APRI, are very effective in identifying moderate-to-advanced fibrosis in this high-risk population[26].

A few caveats should be highlighted. The authors did not intend to suggest a screening strategy for the "real world" but rather assess the performance in risk groups and testing against liver histology in patients recruited at a tertiary university hospital research setting, as this was not a population-based screening study. Many had elevated plasma ALT and the cutoffs chosen (i.e., ≥ 30 IU/L for males and ≥ 19 IU/L for females) were lower than those in clinical practice (e.g., ≥ 40 U/L), enhancing the sensitivity and overall performance of the liver biochemistry approach. However, most patients in primary care settings have ALT < 40 U/L. Because plasma ALT > 30 U/L is associated with increased liver morbidity and mortality, as a practical approach for clinicians, the clinical practice guidelines have recently chosen as a practical approach for clinicians a lower ALT (> 30 U/L) for both genders as a high-risk group for NAFLD and advanced fibrosis[29]. While APRI > 0.50 performed well overall and was comparable to FIB-4 > 1.3, it should be noted that the specificity and overall performance of FIB-4 can be improved for FIB-4 using higher cutoffs (e.g., 1.67)[28]. Liver assessment is nowadays widely done in the clinic by transient elastography and measurement of liver content fat by MRI-based techniques is not recommended (also done by the investigators as part of research studies). Finally, HOMA-IR was also part of the research setting of the investigators but should not be at present part of a routine NAFLD screening strategy as there is significant variability among insulin assays by clinical laboratories, which will diminish its performance in the real world.

In conclusion, for overweight and obese patients with metabolic syndrome and suspected NAFLD, screening for advanced hepatic fibrosis is warranted using noninvasive tests for this purpose, e.g., FIB-4 or APRI. Targeting screening of patients with elevated ALT levels using FIB-4 or APRI provides the most cost-effective first-line approach [Figure 1]. Still, because in most patients plasma aminotransferases are not elevated[26-28], current guidelines[24,29] recommend FIB-4 (over APRI or NFS) to identify advanced fibrosis in high-risk patients given the superior screening and long-term outcomes predictive value of FIB-4[29-31]. Future research is warranted to better stratify subjects with suspected NAFLD regarding duration of diabetes, quality of blood glucose control and body fat distribution.

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The author contributed solely to the article.

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