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Early Detection of Alcoholic Liver Disease: Are We a Step Closer?

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Alcoholic liver disease (ALD) is a growing cause of liver-related morbidity and mortality worldwide.[1] Rates of hazardous drinking are increasing, the age of onset of drinking is decreasing, and more women are drinking heavily.[2] With better control of chronic hepatitis B and C, ALD is again becoming one of the commonest causes of chronic liver disease.[1] ALD comprises a spectrum of clinical and pathologic features, ranging from minimal abnormalities, such as steatosis, to more severe liver disease associated with inflammation, as in alcoholic hepatitis (AH), advanced fibrosis, or cirrhosis.[3] Many patients who drink excessively are diagnosed when their liver disease decompensates, suggesting an asymptomatic period of fibrosis or compensated cirrhosis.[4] If so, this would support a screening strategy to identify those at risk. In this issue of *Gastroenterology*,[5] Thiele et al report on the usefulness of transient elastography (TE) using Fibroscan or 2-dimensional shear wave elastography (2D-SWE, Aixplorer) in detecting fibrosis/cirrhosis in heavy drinkers, using liver biopsy as the gold standard.

Screening for ALD makes intuitive sense. The National Institute on Alcohol Abuse and Alcoholism reported that there are 16.6 million American adults with alcohol use disorders (AUDs). The public health approach to hazardous drinking is early screening, brief intervention, and referral to treatment starting in adolescence.[3] The main target of this strategy is those drinking at hazardous but not yet dependent levels, when success rates are best.[6] This approach is not only cost effective, but actually cost saving, because screening is rapid and inexpensive.[6] Screening for ALD is more complicated but may be warranted. Jinjuvadia and Liangpunsakul[7] reported an increase in total number of AH-related hospitalizations from approximately 250,000 in 2002 to approximately 326,000 in 2010. The majority of patients with AH have fibrosis or cirrhosis on biopsy,[8] a fairly high percentage are unable to abstain, and thus a large number of these patients will likely progress to cirrhosis.

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Conflicts of interest

The authors disclose no conflicts.

Although ALD is common in absolute terms, it seems to be an uncommon consequence of AUDs.[9] Based on these epidemiologic data, AH patients may represent approximately 1%–2% of the total numbers of heavy drinkers.[7] Cirrhosis deaths affect only 0.2% of those with AUDs, and only about 10%–15% of people with AUDs develop cirrhosis in their lifetime.[7] Thus, ALD develops in only a small minority of excessive drinkers; this low prevalence of disease among a large population of at-risk individuals makes cost-effective screening more difficult, especially given the social and economic barriers patients with AUDs have that impede linkage with providers.[10]

An approach used to guide screening is risk stratification. Unfortunately, there are no clinical parameters or diagnostic tests that can accurately predict the development of ALD. Risk factors include female sex, nutritional deficiency, dietary components (type of fat and caffeine), genetic factors (eg, *PNPLA3* genotype), smoking, and obesity, but we lack a model that accurately predicts ALD, nor do quantity, frequency, pattern or type of alcohol consumed predict risk.[11] Laboratory tests such as aspartate transaminase to alanine transaminase ratio are not useful as most subjects with AUDs do not have a high ratio or even increased aminotransferase levels.[12]

A possible approach to early identification of ALD is TE. Thiele's group recruited heavy drinkers from 2 general venues in Denmark, based on the pretest probability of alcohol-related cirrhosis: liver clinics (high pretest risk; n = 128) and municipal alcohol rehabilitation centers (low pretest risk; n = 71).[5] Nearly all of these patients underwent liver biopsy on the same day as TE. Patients referred to the liver clinics with obvious cirrhosis were excluded. Thirty-nine (30%) and 33 (26%) of high pretest risk subjects and 9 (12%) and 3 (4%) of the low pretest group had advanced fibrosis and cirrhosis, respectively.[5] About one-half of the subjects were abstinent at enrollment, and of these, 70% had stopped drinking for <12 months (median, 10 weeks). The results of this study were as follows. (1) Fibroscan and 2D-SWE had a high diagnostic accuracy for advanced fibrosis and cirrhosis in heavy drinkers and the performance of the 2 methods was comparable. (2) The optimal cutoff values for advanced fibrosis and cirrhosis were different depending on the pretest probability of alcohol-related cirrhosis. (3) Both methods had very high negative predictive value. Only 2 of 199 patients with low liver stiffness (LS) had cirrhosis on biopsy. However, the positive predictive value was less impressive, ranging from 49% to 73%, depending on the pretest probability of cirrhosis. (4) Both methods correlated well with the collagen proportionate area determined on the liver biopsy samples. Finally, (5) by including an additional cohort of patients with decompensated alcohol-related cirrhosis (Child-Pugh classes B and C) enrolled from a hospital in Germany, both TE and 2D-SWE were excellent in differentiating subjects with Child-Pugh class A from those with B and C disease, but not Child B from C.

This study is perhaps the largest to explore the use of Fibroscan and 2D-SWE to screen for advanced fibrosis and cirrhosis, especially in heavy drinkers without other evidence of ALD.[5] A few observations deserve comment. First, contrary to other reports,[13,14] this study did not observe an effect of heavy drinking on LS. However, this was based entirely on the patients' self-reported alcohol use, and only 11 patients admitted to heavy drinking. A previous study showed LS decreased significantly in nearly one-half of heavy drinkers after

7 days of abstinence, which was ensured by hospitalizing the patient.[13] Second, the optimal cutoff for LS to predict advanced fibrosis and cirrhosis is considerably higher than that for hepatitis C virus.[15] Thiele et al[5] suggested that it may relate to the different pattern of fibrosis between ALD and hepatitis C virus. Last, they suggested the LS in advanced ALD might be influenced by cholangiocyte injury, because LS correlated with bilirubin and glutamyl transpeptidase.[5] Although extrahepatic cholestasis can increase LS, irrespective of fibrosis,[16] it is not clear why another marker of cholestasis, alkaline phosphatase, was not correlated. It is possible that the association with GGT reflects undisclosed heavy alcohol use by the patients, which in turn would suggest that heavy alcohol use indeed increases the LS. Another possibility is an unrecognized association between AH and LS; the authors are urged to review their biopsy specimens to test this hypothesis. Either way, it seems the most reliable estimates of LS will be obtained while the patient is abstinent.

The findings from this study are an important impetus for attempts at identifying patients at an earlier stage of ALD. Fully 17% of the low-risk heavy drinking patients had advanced fibrosis or cirrhosis; this unexpectedly high yield compares favorably with other conditions in which screening is practiced (lung cancer, prevalence of 0.5%–2.2% in smokers[17]; hepatoma, 3%–8% per year in patients with cirrhosis from hepatitis C and B virus infection[18]). Early identification of such patients will only be valuable if we can influence their drinking behavior with either cognitive or pharmacologic treatments, because we lack treatment that prevents liver injury with continued drinking. There is evidence that this is possible: alerting patients of possible ALD (using blood tests for fibrosis) reduced their drinking levels at their 1-year follow-up.[19] One could envision tailoring brief or more intensive treatment to patients with evidence of fibrosis from TE. For those with cirrhosis, there is still considerable impact of reduced drinking on survival and outcome. The 5-year survival rate for people with cirrhosis who stop drinking is about 90%, compared with 70% for those who continue to drink.[20] Even after the development of complications from cirrhosis, abstinence is essential, because the survival rate is approximately 60% for those who stop drinking and 35% for those who do not.[20]

Much information would be needed before widespread screening with TE could be considered. Knowledge of the alcohol drinking trajectory in the low risk patients of the Thiele study[5] might help to determine when screening is needed, that is, what was the quantity and duration of heavy alcohol use which was associated with advanced fibrosis and cirrhosis? Longitudinal studies of heavy drinkers would help us to understand the time course of the development of fibrosis. It is assumed that patients have gradual development of fibrosis, but it is possible that it develops rapidly, for instance, during a clinical or subclinical episode of AH. This might explain why we so often identify the patients only when they decompensate, and would seriously impact the ability of screening for fibrosis to prevent cirrhosis. Other important outstanding questions include the following. Can we confirm that early detection of advanced fibrosis influences the patient’s ability to abstain long term? Does early detection of advanced fibrosis and abstinence result in reversal of fibrosis, as is seen with the control of chronic viral hepatitis? And, of course, does early detection of advanced fibrosis and cirrhosis prolong the patients’ lives, reduce medical expenses, and improve quality of life? Nonetheless, the dissemination of TE technology may provide a way for primary care physicians, hepatologists, and addiction specialists to focus

care on patients with AUDs at the greatest risk of advanced liver disease, and reduce this serious complication of heavy alcohol use.

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