

NASH-Related Cirrhosis: An Occult Liver Disease Burden

SEE ARTICLE ON PAGE 53

Nonalcoholic fatty liver disease (NAFLD) is reaching epidemic proportions. It is currently the most common cause of chronic liver disease worldwide, with a prevalence of 25%-30% of the general population.⁽¹⁾ Recent estimates indicate that over 64 million people may have NAFLD in the United States while Europe has an estimated 53 million affected individuals.⁽²⁾ These figures point to a daunting and enormous disease burden of NAFLD that is closely related to the obesity epidemic and has an impact on mortality as patients with NAFLD exhibit an increased risk of death compared to the general population.⁽³⁾ Although cardiovascular disease is the leading cause of death in patients with NAFLD, the

development of nonalcoholic steatohepatitis (NASH), the progressive form of NAFLD that affects 10%-15% of patients with the disease, determines the increased rates of liver-related mortality due to the development of cirrhosis and its complications, including hepatocellular carcinoma (HCC).⁽⁴⁾

Despite its high prevalence and potentially serious consequences, awareness about NAFLD is limited among nonspecialists. Several studies^(5,6) have shown that NAFLD is not regarded as a clinically important diagnosis by a significant proportion of providers. These providers underestimate disease prevalence among their patients and do not identify those factors associated with more serious or advanced disease⁽⁷⁾; the latter will lead to unfocused management, limited referral of patients to hepatology clinics, and eventually to a lack of recognition of advanced liver disease. Since patients with cirrhosis represent an at-risk population for complications such as portal hypertension-associated complications and HCC, an untimely diagnosis may impact a patient's outcome.

In the first issue of *Hepatology Communications*, Bertot et al.⁽⁸⁾ report their results of a retrospective study of a prospectively collected cohort of 100 patients with NAFLD-related cirrhosis. Their aim is to establish the mode of diagnosis (incidental versus intentional) and its association with liver-related complications, particularly HCC. Interestingly, in two thirds of patients, cirrhosis was diagnosed incidentally and was more likely to have concomitant HCC than in those patients who had been diagnosed intentionally with cirrhosis (12% versus 0%, respectively, $P < 0.05$). In addition, when reviewing their medical records, a significant proportion of these patients had thrombocytopenia and splenomegaly as markers of chronic liver disease. Moreover, when available noninvasive fibrosis scores were calculated, results pointed to the presence of advanced fibrosis in a significant percentage of individuals included in the study. Thus, this work shows that the diagnosis of cirrhosis and advanced fibrosis in the setting of NAFLD is frequently missed by physicians and that several simple scores would have helped to provide an earlier diagnosis.

Abbreviations: GI, gastrointestinal; HCC, hepatocellular carcinoma; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

Received March 13, 2017; accepted March 16, 2017.

Partially supported by research grants from the Fondo Nacional de Desarrollo Científico y Tecnológico (FONDECYT 1150327 to M.A.), the Comisión Nacional de Investigación Científica y Tecnológica (grant CONICYT PIA/Basal PFB12, Basal Centre for Excellence in Science and Technology to M.A.), and National Institutes of Health grants R01 DK082451 and U01 AA022489 (to A.E.F.)

Copyright © 2017 The Authors. *Hepatology Communications* published by Wiley Periodicals, Inc., on behalf of the American Association for the Study of Liver Diseases. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

View this article online at wileyonlinelibrary.com.

DOI 10.1002/hep4.1033

Potential conflict of interest: Nothing to report.

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO:

Ariel E. Feldstein, M.D.
 Department of Pediatrics
 University of California San Diego
 9500 Gilman Drive, MC 0715
 La Jolla, CA 92037-0715, USA
 E-mail: afeldstein@ucsd.edu
 Tel.: +1-858-966-8907

The study of Bertot et al.⁽⁸⁾ underscores a problem of enormous relevancy considering the more than 60 million people estimated to have NAFLD in the United States.⁽²⁾ Although the general population prevalence of NASH-related cirrhosis remains unknown, extrapolation from the available epidemiological data suggests that the population at risk (i.e., NASH with fibrosis) may reach to more than 4 million adult Americans. Of note, a recent study suggests that the prevalence of NASH-related cirrhosis and fibrotic NAFLD has increased 2.5-fold and 2-fold, respectively, in the United States, which is in line with the observation that NASH-related cirrhosis is surpassing hepatitis C virus-related cirrhosis as the top etiology for adults listed for liver transplantation in that country.⁽⁹⁾ Thus, NASH-related cirrhosis is increasing as a medical problem, and given the lack of awareness of NAFLD, it is likely that the real disease burden of this condition remains hidden.

What can be done to increase awareness about NAFLD and its consequences? The role of liver-related scientific societies is of utmost importance. Although, these societies devote significant effort to educating their members through special conferences, seminars, articles, and books, in our opinion more needs to be done to disseminate knowledge about the disease among non-gastrointestinal (GI) non-hepatology physicians (e.g., endocrinologists, general practitioners, and cardiologists). Due to the multisystem nature of NAFLD⁽¹⁰⁾ and the coexistence of other conditions, such as diabetes, heart disease, psoriasis, polycystic ovary disease, and others,⁽¹¹⁾ those non-GI non-hepatology physicians routinely following patients with NAFLD sometimes do not identify NAFLD as a clinically important diagnosis or do not have the appropriate competences to recognize people at risk of progression or patients with already established cirrhosis. The latter determines whether patients get a delayed or no referral to hepatology clinics.⁽⁵⁾ Thus, targeted education activities directed to non-GI non-hepatology physicians should be intensified to increase awareness about the disease. These activities should stress the clinical relevancy of NAFLD and the usefulness of clinical and laboratory data, including the use of composite scores (i.e., NAFLD fibrosis score, fibrosis-4, and others) to identify patients at risk for more serious or advanced disease.⁽¹²⁾ It should also be stressed that, when available, the use of transient elastography has an important role in the appropriate stratification of patients with NAFLD with regards to the presence of fibrosis or cirrhosis.⁽¹³⁾ One of the main

target audiences of these efforts should be the physicians that follow patients with diabetes. As commented by Bertot et al., recent studies have shown a high prevalence of undiagnosed advanced fibrosis and cirrhosis in patients with diabetes, demonstrating that NAFLD is an important health threat to individuals with diabetes.⁽¹⁴⁾ Nevertheless, recent guidelines from the American Diabetes Association include only a short paragraph on NAFLD without any recommendations on screening, diagnostic, or therapeutic actions.⁽¹⁵⁾

In conclusion, the report of Bertot et al. is important because it underlines a common problem faced by hepatologists, which is unrecognized cirrhosis in patients with NAFLD. Given that current scientific information supports the use of tools (i.e., clinical parameters, composite scores, and elastography techniques) that allow appropriate stratification of patients with NAFLD and that help provide an early diagnosis of cirrhosis, education on NAFLD diagnosis and staging among all physicians caring for patients with this condition should be intensified. More dialogue is also needed between liver scientific societies and those societies whose membership includes health providers who are likely to encounter patients with NAFLD in their practice. Finally, a need for consensus on when and how to screen for the disease is needed. The consequences from inaction on this may be tremendous considering the increasing burden of NAFLD worldwide.

Marco Arrese¹

Ariel E. Feldstein²

¹Department of Gastroenterology,
Escuela de Medicina

Pontificia Universidad Católica de Chile
Santiago, Chile

²Department of Pediatrics

University of California
San Diego, CA

REFERENCES

- 1) Sayiner M, Koenig A, Henry L, Younossi ZM. Epidemiology of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis in the United States and the rest of the world. *Clin Liver Dis* 2016;20:205-214.
- 2) Younossi ZM, Blissett D, Blissett R, Henry L, Stepanova M, Younossi Y, et al. The economic and clinical burden of nonalcoholic fatty liver disease in the United States and Europe. *Hepatology* 2016;64:1577-1586.
- 3) Adams LA, Lymp JF, St Sauver J, Sanderson SO, Lindor KD, Feldstein A. The natural history of nonalcoholic fatty liver

- disease: a population-based cohort study. *Gastroenterology* 2005;129:113-121.
- 4) Satapathy SK, Sanyal AJ. Epidemiology and natural history of nonalcoholic fatty liver disease. *Semin Liver Dis* 2015;35:221-235.
 - 5) Bergqvist CJ, Skoien R, Horsfall L, Clouston AD, Jonsson JR, Powell EE. Awareness and opinions of non-alcoholic fatty liver disease by hospital specialists. *Intern Med J* 2013;43:247-253.
 - 6) Ghevariya V, Sandar N, Patel K, Ghevariya N, Shah R, Aron J, et al. Knowing what's out there: awareness of non-alcoholic fatty liver disease. *Front Med (Lausanne)* 2014;1:4.
 - 7) Wieland AC, Quallick M, Truesdale A, Mettler P, Bambha KM. Identifying practice gaps to optimize medical care for patients with nonalcoholic fatty liver disease. *Dig Dis Sci* 2013;58:2809-2816.
 - 8) Bertot LC, Jeffrey GP, Wallace M, MacQuillan G, Garas G, Ching HL, et al. Nonalcoholic fatty liver disease-related cirrhosis is commonly unrecognized and associated with hepatocellular carcinoma. *Hepatol Commun* 2017;1:53-60.
 - 9) Kabbany MN, Conjeevaram Selvakumar PK, Watt K, Lopez R, Akkas Z, Zein N, et al. Prevalence of nonalcoholic steatohepatitis-associated cirrhosis in the United States: an analysis of National Health and Nutrition Examination Survey data. *Am J Gastroenterol* 2017; doi: 10.1038/ajg.2017.5.
 - 10) Byrne CD, Targher G. NAFLD: a multisystem disease. *J Hepatol* 2015;62:S47-64.
 - 11) VanWagner LB, Rinella ME. Extrahepatic manifestations of nonalcoholic fatty liver disease. *Curr Hepatol Rep* 2016;15:75-85.
 - 12) Rinella ME, Sanyal AJ. Management of NAFLD: a stage-based approach. *Nat Rev Gastroenterol Hepatol* 2016;13:196-205.
 - 13) European Association for Study of Liver, Asociacion Latinoamericana para el Estudio del Hgado. EASL-ALEH Clinical Practice Guidelines: non-invasive tests for evaluation of liver disease severity and prognosis. *J Hepatol* 2015;63:237-264.
 - 14) Bril F, Cusi K. Management of nonalcoholic fatty liver disease in patients with type 2 diabetes: a call to action. *Diabetes Care* 2017;40:419-430.
 - 15) Marathe PH, Gao HX, Close KL. American Diabetes Association Standards of Medical Care in Diabetes 2017. *J Diabetes* 2017;9:320-324.