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NASH-RELATED CIRRHOSIS: AN OCCULT LIVER DISEASE BURDEN

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Nonalcoholic fatty liver disease (NAFLD) is reaching epidemic proportions currently being 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 US while in Europe the estimate is of 53 million affected individuals (2). These figures, indicate a daunting and enormous disease burden of NAFLD, which is closely related to the obesity epidemics and has impact in 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 NAFLD patients, the development of non-alcoholic steatohepatitis (NASH), the progressive form of NAFLD that affects 10–15% of patients with the disease, determines increased rates of liver-related mortality due the development of cirrhosis and its complications including hepatocellular carcinoma (HCC) (4).

In spite of its high prevalence and potentially serious consequences, awareness about NAFLD is limited among non-specialists. Several studies (5, 6) have shown that NAFLD is not regarded as a clinically important diagnosis by a significant proportion of providers who underestimate disease prevalence among their patients and do not identify those factors associated with more serious or advanced disease (7). The latter determines a non-focused management and limited referral of patients to hepatology clinics and, eventually, to 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 hepatocellular carcinoma (HCC) an untimely diagnosis may impact on patient's outcomes.

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 aiming to establish the mode of diagnosis (incidental vs.

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intentional) and the association of this with liver-related complications, particularly HCC. Interestingly, in 2/3 of patients, cirrhosis was diagnosed incidentally and was more likely to have concomitant HCC than in those patients in whom cirrhosis diagnosis was intentional (12% versus 0%, $P < 0.05$). 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 non-invasive fibrosis scores were calculated and 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, if used, several simple scores would have helped to an earlier diagnosis.

The study of Bertot et al. (8) underscores a problem of enormous relevancy considering that about 64 million of people in the US are estimated to have NAFLD (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 up to more than 4 million of adult Americans. Of note, a recent study suggest that the prevalence of NASH-related cirrhosis and fibrotic NAFLD has increased 2.5-fold and 2-fold respectively in the U.S., 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 rising as a medical problem and, given the lack of awareness of NAFLD, it is likely that the real disease burden of this condition remains occult.

What can be done to increase awareness about NAFLD and its consequences? The role of liver-related scientific societies is of utmost importance. Although, they devote significant efforts to educate their members through special conferences, seminars, articles, books etc., in our opinion, more needs to be done with regard to the dissemination of knowledge about the disease among non-GI, non-hepatology physicians (endocrinologists, general practitioners, cardiologists, etc.). 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 a delayed or no referral of patients 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, FIB-4, and others), to identify patients at risk for more serious or advanced disease (12). Also, it should 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 diabetic patients. As commented by Bertot et al., recent articles have shown a high prevalence of undiagnosed advanced fibrosis and cirrhosis in diabetic patients showing that NAFLD is an important health threat to diabetic individuals (14). In spite of that, 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 since underlines a common problem faced by hepatologists that is the unrecognized cirrhosis in patients with NAFLD. Given that current scientific information supports the use of a set of tools (i.e. clinical parameters, composite scores and elastography techniques) that allow to appropriately stratify NAFLD patients and to diagnose cirrhosis early in the course of the disease, education on NAFLD diagnosis and staging among all physicians caring patients with this condition should be intensified. Also, more dialogue is needed between liver scientific societies and those societies that group health providers likely to encounter NAFLD patients 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 looming increase in the burden of NAFLD worldwide.

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Abbreviations

NAFLD	Nonalcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
HCC	hepatocellular carcinoma

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