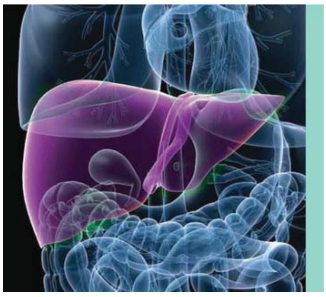

The Epidemiology of Nonalcoholic Steatohepatitis

Zobair M. Younossi, M.D., M.P.H., F.A.A.S.L.D. *,†

The growing global epidemic of obesity has led the World Health Organization (WHO) to estimate that, in 2016, more than 1.9 billion adults (39% of the adult population) were overweight, and 650 million (13% of adult population) were considered obese.[1] In the United States, the data from the National Health and Nutrition Examination Survey for 2013 to 2014 estimated that an even higher proportion of the adults was overweight (32.5%), obese (37.7%), and extremely obese (7.7%).[1] As these global rates of obesity increase, obesity-related complications are also on the rise. Of these, nonalcoholic fatty liver disease (NAFLD) is becoming one of the most important causes of liver disease throughout the world,[2-4] with an estimated global prevalence rate of about 24%.[3] In fact, the highest prevalence of NAFLD has been reported from South America and the Middle East, whereas the lowest prevalence has been reported from Africa (Fig. 1).[3-6] Because the diagnosis of the subtype of NAFLD, or nonalcoholic steatohepatitis (NASH), requires histological confirmation, the prevalence of NASH in the general population can only be estimated from a few biopsy series. This prevalence rate ranges between 1.5% and 6.45%.[3-6] Although there are reasonably accurate data for the prevalence of NAFLD in the general population, the data about the incidence of NAFLD and NASH from the general population is lacking. In this context, it has been estimated that the incidence of NAFLD varies across the world, ranging from 28.01 per 1000 person-years (95% confidence interval [CI]: 19.34-40.57) to 52.34 per 1000 person-years (95% CI: 28.31-96.77).[2,3]

There is substantial evidence that most patients with NAFLD have some components of metabolic syndrome (MS) including central obesity, insulin resistance, dyslipidemia, and hypertension.[3] In fact, there is a bidirectional association between MS and NAFLD.[2,3] Focusing on high-risk groups, you would expect to see a higher prevalence of NAFLD in those enriched with risk factors. In this context, there is a higher prevalence of MS in patients with NAFLD and more NAFLD in patients who fulfill the criteria for MS.[2-4] In addition, a number of complications of MS

Abbreviations: CI, confidence interval; HCC, hepatocellular carcinoma; MS, metabolic syndrome; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; OSA, obstructive sleep apnea; T2DM, type 2 diabetes mellitus; WHO, World Health Organization.

From the *Center for Liver Disease, Department of Medicine, Inova Fairfax Hospital, Falls Church, VA, and †Betty and Guy Beatty Center for Integrated Research, Inova Health System, Falls Church, VA.

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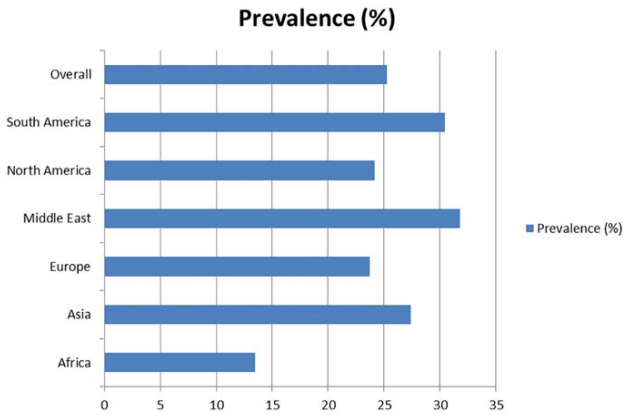

FIG 1 Prevalence of NAFLD in different regions of the world.

(cardiovascular disease, obstructive sleep apnea [OSA]) are highly prevalent in patients with NAFLD.[2-4] Furthermore, NAFLD is an independent predictor for cardiovascular disease and cardiovascular mortality, and in turn, cardiovascular mortality is the most common cause of death among patients with NAFLD and NASH.[2-4] Also, OSA, another complication of MS, is highly prevalent in NAFLD, and these patients are three times as likely to have NASH compared with patients without OSA.[2,6,7]

One group at the greatest risk for NAFLD and NASH are those with type 2 diabetes mellitus (T2DM). A recent meta-analysis suggests that the global NAFLD prevalence rate among patients with T2DM is 57.80% (95% CI: 53.88%-61.62%), whereas the prevalence of NASH among the patients with T2DM who underwent biopsy is 65.26% (95% CI: 51.73%-76.71%).[8]

It has been suggested that the hepatic expression of NAFLD can be modified by genetic or environmental factors. Although the components of MS are quite common in African Americans, NAFLD and especially its progressive form, or NASH, is less common in African Americans as compared with white and Hispanic populations.[4] In contrast, the increased risk for NASH and related fibrosis in Hispanic Americans has been of great interest. Although initially it was thought that all Hispanics are at high risk for NAFLD and NASH, more recent data suggest a potential role for the country of origin. In fact, the prevalence rate of NAFLD in Hispanics of Mexican origin is estimated at 33% as compared with Hispanics from Dominican (16%) or Puerto Rican (18%) origins.[9] These data suggest a complex interplay between environmental and genetic factors that can influence the expression of the NASH phenotype and its progression (Fig. 2). In this context, these factors must be considered when studying the epidemiology of NAFLD and NASH.[6]

Finally, it is important to recognize that NAFLD and NASH can occur in the absence of obesity. Although NAFLD is more common in obese individuals, the prevalence rate of NAFLD in lean individuals in the United States is about 7%, whereas prevalence rates in rural areas of some Asian countries can be as high as 25% to 30%.[2-6,9]

The natural history of NAFLD is also quite interesting and evolving. A number of cohort studies have suggested that NASH is the predominant type of NAFLD that can progress.[2] In this context, about 10% to 15% of patients with NASH progress to cirrhosis.[2-6] This progression is nonlinear and, in fact, some patients with NASH, even those with fibrosis, may spontaneously regress.[4] Although most

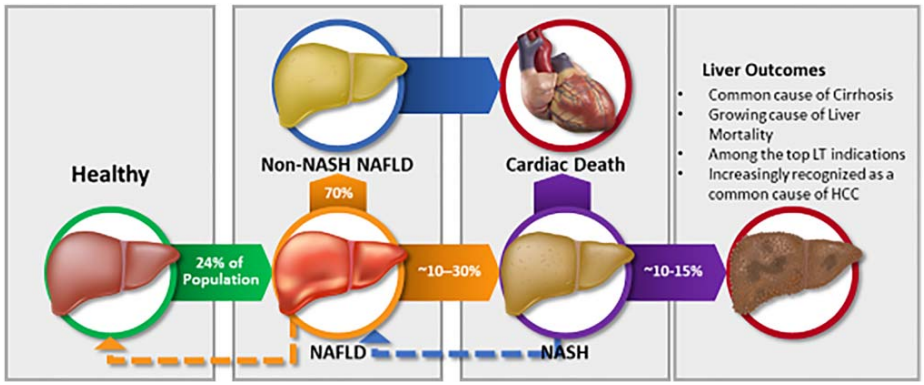

FIG 2 A simplified version of the natural history of NAFLD and NASH.

patients with the non-NASH type of NAFLD do not progress, a few actually do progress to NASH and even cirrhosis.[4] Notwithstanding the fact that cardiovascular mortality is the most common cause of death among patients with NAFLD and NASH, liver-related complications are quite common in these patients and liver-related mortality is among the top three causes of death (Fig. 2).[2-9] Due to the enormous number of patients with NASH in the general population, the number of patients with NASH with cirrhosis and hepatocellular carcinoma (HCC) who become candidates for liver transplantation has been rapidly growing.[10-13] Although there are no accurate surrogates to predict liver-related or all-cause mortality in NASH, it seems that increasing the number of components of MS, especially T2DM in patients with NASH, is an independent predictor of liver-related mortality.[2,4,13] In addition, presence of stage 2 or higher hepatic fibrosis, as determined by liver biopsy, is also another independent predictor of mortality.[13] As better prognostic biomarkers for NASH are developed and validated, it may be possible to predict which individuals with NASH are at highest risk for adverse outcomes without a liver biopsy.

In summary, the prevalence of the NAFLD spectrum is rapidly growing throughout the world. Given the sheer number of patients with NAFLD and the progressive subtype of NASH, the potential hepatic consequences are enormous. Already, NASH is among the top three indications for liver transplantation in the United States due to decompensated liver disease. In addition, NASH is the most rapidly growing cause of HCC in the United States. Given the lack of pharmacological therapy for NASH and no effective national policy to address the epidemic of obesity and T2DM, there is no doubt that the clinical, economic, and patient-reported burden of NASH in the United States and the rest of the world will continue to grow.[14,15]

CORRESPONDENCE

Zobair M. Younossi, M.D., M.P.H., F.A.A.S.L.D., Betty and Guy Beatty Center for Integrated Research, Claude Moore Health Education and Research Building, 3300 Gallows Road, Falls Church, VA 22042. E-mail: zobair.younossi@inova.org

REFERENCES

1) GBD 2015 Obesity Collaborators; Afshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K, et al. Health effects of overweight and obesity in 195 countries over 25 years. N Engl J Med 2017;377:13-27.

2) Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. Hepatology 2018;67:328-357.

3) Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease: meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 2016;64:73-84.

4) Younossi ZM, Loomba R, Anstee QM, Rinella ME, Bugianesi E, Marchesini G, et al. Diagnostic modalities for non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH) and associated fibrosis. Hepatology; doi:10.1002/hep.29721.

5) Younossi ZM, Loomba R, Rinella ME, Bugianesi E, Marchesini G, Neuschwander-Tetri BA, et al. Current and future therapeutic regimens for non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH). Hepatology; doi:10.1002/hep.29724.

6) Younossi Z, Anstee QM, Marietti M, Hardy T, Henry L, Eslam M, et al. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol 2018;15:11-20.

7) Anstee QM, Targher G, Day CP. Progression of NAFLD to diabetes mellitus, cardiovascular disease or cirrhosis. Nat Rev Gastroenterol Hepatol 2013;10:330-344.

8) Younossi ZM. AASLD Liver Learning Oct 23, 2017; 195652. Accessed from http://liverlearning.aasld.org/aasld/2017/thelivermeeting/195652/zobair.younossi.burden.of.illness.economic.model.for.patients.with.html

9) Sayiner M, Koenig A, Henry L, Younossi Z. 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.

10) Wong RJ, Aguilar M, Cheung R, Perumpail RB, Harrison SA, Younossi ZM, Ahmed A. Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States. Gastroenterology 2015;148:547-555.

11) Goldberg D, Ditah IC, Saeian K, Lalehzari M, Aronsohn A, Gorospe EC, Charlton M. Changes in the prevalence of hepatitis C virus infection, nonalcoholic steatohepatitis, and alcoholic liver disease among patients with cirrhosis or liver failure on the waitlist for liver transplantation. Gastroenterology 2017;152:1090-1099.e1.

12) Younossi ZM, Otgonsuren M, Henry L, Venkatesan C, Mishra A, Erario M, Hunt S. Association of nonalcoholic fatty liver disease (NAFLD) with hepatocellular carcinoma (HCC) in the United States from 2004 to 2009. Hepatology 2015;62:1723-1730.

13) Younossi ZM, Otgonsuren M, Venkatesan C, Mishra A. In patients with non-alcoholic fatty liver disease, metabolically abnormal individuals are at a higher risk for mortality while metabolically normal individuals are not. Metabolism 2013;62:352-360.

14) Estes C, Razavi H, Loomba R, Younossi Z, Sanyal AJ. Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease. Hepatology 2018;67:123-133.

15) 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.