



Unmasking a Stealth Killer: The Need for Increased Awareness of NASH

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Awareness of a disease, particularly of a liver disease (LD), before it grows to an epidemic level should be a public health concern for many valid reasons. First, a LD that can arise from lifestyle or from genetic origins may be treated successfully at an early stage when it is suitably diagnosed, tracked by public health officials, and treated by frontline practitioners. Second, the increasing prevalence of obesity in the USA has made awareness of liver diseases such as non-alcoholic fatty liver disease (NAFLD) even more essential for the success of the nation's healthcare system. However, disease awareness must be a two-way street not just in the medical lexicon but also in the public domain. It requires the involvement of both the patient and the physician for the prevention of late-stage liver disease and the restoration of optimal health. In the case of NAFLD, the broad spectrum of liver damage it comprises must be an issue of concern for health administrators and their patients. The deposition of fat droplets in liver hepatocytes causes simple steatosis (i.e., NAFL), which might progress to steatohepatitis (i.e., NASH), an inflammatory stage of the disease in which cytokines and immune cells are involved. The difficulty so far for researchers and policymakers has been the accurate estimation of the prevalence of NAFLD/NASH in the population since these diseases are asymptomatic. Although NAFLD and NASH may be reversed if managed early with profound lifestyle changes including strict adherence to an exercise regimen and a weight reduction diet, the next course of the disease is punctuated by advancing fibrosis that leads to cirrhosis, which is usually irreversible. Years later, the organ may deteriorate into end-stage liver disease (ESLD) or hepatocellular carcinoma, (HCC) often eventuating in liver transplantation or death [1].

NAFLD is sometimes referred to as the hepatic manifestation of the metabolic syndrome (MetS), whose predominant

underlying risk factors include hypertension, high blood glucose levels (insulin resistance), truncal obesity, hypertriglyceridemia, and low circulating levels of high-density lipoprotein (HDL) that increase the prospect of developing diabetes, ischemic heart disease, and stroke [2]. Though the pathogenesis of NAFLD and MetS is complex and multifactorial, the two may share similar pathophysiological mechanisms that underlie insulin resistance as a key factor.

Chronic liver disease (CLD) is a major cause of morbidity, mortality, disease burden, and high cost of healthcare resources worldwide [3]. In the 30 years following 1980, mortality related to CLD increased by 46% worldwide [4]. Currently, NAFLD is rapidly becoming the most common cause of CLD, estimated at 20–30%, whereas NASH is estimated to affect 2–5% of the general population in the USA and around the world primarily due to the prevalence of obesity [5, 6]. More concerning is the prediction that by 2030, the prevalence of NASH will increase by 63% [6]. NASH, which increases the risk of cirrhosis and ESLD, is expected by 2020 to replace hepatitis C viral (HCV) disease as the leading indicator for liver transplantation [7]. These findings should give more weight for the widespread and aggressive nature of NAFLD/NASH, which ironically is getting less notice and awareness than HCV. Therefore, the publication of an article addressing patient awareness of NAFLD by Singh et al. [8] in this issue of *Digestive Diseases and Sciences* is timely. The aim was twofold: to assess (1) awareness of NAFLD and (2) factors associated with being aware of LD in participants of the NHANES study who were suspected of having NAFLD (i.e., BMI > 25 kg/m² and elevated ALT). The article clearly shows that most patients (i.e., 95%) with NAFLD in the USA are not aware that they harbor a liver disease. This lack of awareness should raise major concern and should expedite calls for action in the medical profession. The study attempts to highlight the number of Americans who have NAFLD and other comorbidities—such as type 2 diabetes, obesity, and hypertension—and are largely unaware of their LD. The study also reveals that the trend in awareness within this NAFLD cohort over four time periods is increasing but not at a rate high enough to

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influence changes in lifestyle or redirect national and international health resources.

Awareness is defined in the paper according to an individual's response to specific National Health and Nutrition Examination Survey (NHANES) questions raised in the MCQ160L and MCQ170QL surveys. An "aware" subject under MCQ160L medical questionnaire would only respond "Yes" to the question: "Are you 'aware' of ever having an LD or current LD or have you ever been told by a doctor or other health professional that you had any kind of liver condition?" An MC170QL questionnaire would ask: "Do you still have any kind of liver condition?" An answer of "No" or "Don't know" to MCQ160L or MCQ170L was considered as being "unaware" [8].

The investigators evaluated 7033 suspected NAFLD cases who participated in the continuous NHANES survey for a span of 16 years (i.e., 2001–2016). They assessed NAFLD awareness in 4-year blocks (i.e., 2001–2004, 2005–2008, 2009–2012, and 2013–2016) by including a similar number of participants (close to 2000 per designated period) in order to determine the trend and factors associated with LD awareness among a representative US cohort using multivariable logistic regression analysis [8]. For this study, NAFLD patients were defined, in the absence of secondary causes of hepatic steatosis, as being overweight ($\text{BMI} \geq 25 \text{ kg/m}^2$) with an elevated level of alanine aminotransferase (ALT) or exhibiting an increased hepatic steatosis index ($\text{HSI} \geq 36$) [8]. The exclusion principle also included—among others—excessive alcohol consumption, viral hepatitis infections, and hepatotoxic drugs.

The study revealed that there was no difference in the prevalence of central obesity over the four different time cycles but during two of the periods (from 2001–2004 to 2013–2016), there was a significant increase in obesity, BMI, diabetes, MetS, and hypertriglyceridemia [8]. During the same time cycle, there was a precipitous decline in the percentage of smokers while the prevalence of suspected NAFLD and advanced fibrosis spiked (i.e., from 2001–2004 period to 2013–2016). Awareness of having LD increased over the course of the study period as well. Multivariable regression analysis also showed that older age and having a fewer number of alcoholic drinks per day were associated with being aware of having LD. Among the races, blacks were the least aware of harboring the disease and are less affected by NAFLD than other races [9]. Subjects with higher levels of ALT were more aware of having LD. Similarly, having MetS conferred a twofold greater level of awareness than that observed for those without MetS.

This may be one of the largest studies highlighting the low awareness of having an LD among a representative US population, especially in subjects with suspected NAFLD and advanced fibrosis which borders on cirrhosis. The important findings of this study raise hopes that among subjects with

suspected NAFLD and hepatic steatosis index (HSI) > 36 , there is a onefold increase in awareness of having a LD during the study periods of 2001–2004 to 2013–2016 [$p = 0.03$]. Nevertheless, it is alarming that $> 95\%$ of the adult US population with suspected NAFLD, albeit a high-risk group, is still unaware of having LD, exposing millions of subjects to the ravages of this slowly progressive and ultimately irreversible disease, which in turn exacerbates the overall obesity-driven burden of the disease in the society. Furthermore, the ongoing obesity epidemic, the increasing prevalence of diabetes, and other features of MetS will add to the prevalence of NAFLD, NASH cirrhosis, and NAFLD-associated fibrosis, which is also becoming one of the leading causes of liver transplantation in USA. The outsized unawareness state also defies the lack of robust screening methods for patients during hospital visits and challenges physicians and health administrators to take more proactive measures and promote public health awareness and educational campaigns to reduce ignorance and complacency about LDs in general.

This study also is a good companion to an unrelated study that investigated the awareness of NASH and associated practice patterns among primary care physicians and specialists in the USA. In Polanco-Briceno's published study, 302 physicians consisting of a roughly equal number of primary physicians and GI specialists were surveyed online with a 35-point questionnaire about their awareness of different liver conditions and their current practices [10]. About 50% of the primary care physicians surveyed responded by admitting they were unfamiliar about the differences between NAFLD and NASH even though 58% of them were treating patients with NAFLD or NASH. About 10% of the specialists used drugs to treat these conditions that were not recommended by the current guidelines [10]. This striking unawareness was also evident in another survey of 302 US patients in an outpatient clinical setting where only 18% of respondents were familiar with NAFLD and 67% of these patients were unaware that they had metabolic risk factors [11].

Therefore, although this study is not comprehensive and did not randomly include all segments of the society, it can still serve as a guideline for physicians and the public at large to identify the early clinical symptoms of liver disease and prophylactically control the development of NAFLD at the earliest possible stage. The findings of this study will be important especially for health administrators, primary care physicians, and particularly their patients who lack awareness about the growing burden of NAFLD and its related complications, in addition to helping policymakers and government healthcare organizations, and health insurance companies to promote early screening and detection of NAFLD and other liver diseases.

The challenge with NAFLD and its variations is not merely lack of awareness of the disease, but also lack of a

full understanding of its diagnosis, etiology, pathophysiology, and treatment throughout the community. This deficiency in knowledge or awareness can adversely impact patients, health professionals, health providers, and researchers alike. Most importantly, however, the biggest challenge is to increase awareness and improve education in a multi-pronged approach that could include national advocacy with national public health groups; patient advocacy with patient support groups; and continued basic science research and clinical trials for a full understanding of the disease and to design the and appropriate treatment course.

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