Fatty Liver: Think Globally

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The readers of HEPATOLOGY and many other gastroenterology, general medical, endocrinology, and cardiovascular journals have an increasing appetite for articles on the causes, consequences, and management of fatty liver, particularly that of nonalcoholic fatty liver (NAFL) and its intimate association with visceral adiposity and insulin resistance. NAFL is a disorder of lipid metabolism marked by excessive accumulation of triglycerides in hepatocytes occurring in the absence of excessive alcohol use. (What constitutes "excessive alcohol use" has not been established and is not addressed here.) NAFL encompasses a spectrum of histopathology ranging from simple steatosis to nonalcoholic steatohepatitis (NASH) to cirrhosis, and is now recognized as the most common cause of chronic liver abnormalities in the United States—not unexpected given the current epidemic of obesity in this industrialized nation. Although simple steatosis is a relatively innocuous hepatic lesion with low risk for progressive liver disease, NASH has the potential to progress to fibrosis, cirrhosis, and end-stage liver disease, and may be the precursor lesion underlying a substantial proportion of cases of cryptogenic cirrhosis. Less clear is whether NAFL increases the risk of overall mortality and cardiovascular disease mortality independently of other cardiovascular risk factors. In this editorial, we refer consistently to NAFL rather than the commonly used term nonalcoholic fatty liver disease (NAFLD). To call a condition a disease when it is present in a third or more of some populations (Fig. 1) requires a high standard of evidence that has not yet been achieved.

The true prevalence of NAFL in the general population anywhere in the world remains incompletely defined, because there are currently no accurate and noninvasive tests useful for population screening. Therefore, estimates of the prevalence of NAFL are derived either from select patient populations that have undergone liver biopsy or from general population studies primarily based on radiographic imaging consistent with fatty infiltration of the liver. This latter approach was applied in the study by Das and colleagues in this issue of HEPATOLOGY.[1] Although NAFL is well-known in developed countries and is typically associated with the "industrialized" or "Western" lifestyle of low physical activity, calorically dense diet, and obesity, an implication of the study from West Bengal, India, is that NAFL is likely to be more common throughout the world than has been appreciated. The work of Das and colleagues highlights two important issues: (1) NAFL is prevalent among individuals in a developing country who, at cursory glance, may not appear to harbor the typical metabolic risk factors for NAFL and may, therefore, be inappropriately perceived to not be at risk for the condition; and (2) NAFL in this West Bengal population is, indeed, similar to NAFL occurring in other populations with respect to both its metabolic associations and the histological description and consequences.

To those in the Western world, and especially the United States where the common phenotype of the patient with fatty liver is obese, sedentary, and likely to consume alcohol, the most remarkable finding of the current study may be that 8.5% of this population in rural West Bengal had fatty liver without being either alcohol consumers or overweight or obese—at least by Western standards. Physical activity of this population was not described, but 59% of individuals in the study were either agricultural workers or manual laborers and, therefore, likely engaged in considerably greater daily physical activity than the average North American with NAFL. The mean body mass index (BMI) of the West Bengal population was just 19.6 kg/m^2 and 23.0 kg/m^2 among individuals with NAFL. Figure 1 demonstrates the relationship between population BMI and either NAFL or overall fatty liver prevalence (without exclusion of persons who consumed alcohol) from countries around the world. The current study is at the far low end of the spectrum of BMI, but still demonstrated a significant prevalence of NAFL.

This West Bengal study's finding of NAFL occurring in individuals with relatively low BMI and waist circumference adds support to the concern of an increased risk of diabetes and cardiovascular disease

Abbreviations: BMI, body mass index; NAFL, nonalcoholic fatty liver; NASH, nonalcoholic steatohepatitis; OR, odds ratio.

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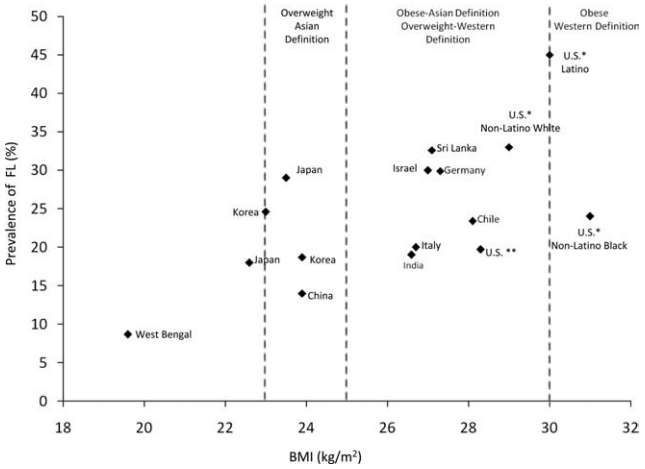

Fig. 1. Estimated prevalence of fatty liver (FL) from selected populations according to country and mean body mass index (BMI) of the population studied.[1,9-21] All studies are based on ultrasonography except: *Radiographic diagnosis of NAFL based on magnetic resonance spectroscopy; ** Radiographic diagnosis of NAFL based on computed tomographic imaging among "healthy" men.

among "normal weight" (by Western standards) residents of Asia, in particular among residents of India. Such concern is manifested in recent efforts to harmonize the definition of the metabolic syndrome, which is based on a correlated set of easily obtained laboratory and body measures and their ability to predict the development of cardiovascular disease.[2] Whereas there is now agreement with respect to the components of the metabolic syndrome, a sticking point has been the appropriate thresholds that should be used for elevated waist circumference. Risk of cardiovascular disease appears to be increased at lower waist circumference among Asian Indians compared with Western populations. Thus, waist circumference thresholds of 80 cm for women and 90 cm for men have been recently recommended among Asian Indians, versus the commonly used standards in the Western world of 88 cm for women and 102 cm for men. Similarly, lower thresholds of BMI of 23 kg/m^2 for overweight and 25 kg/m^2 for obesity have been accepted among Asian Indians than the BMI thresholds of 25 kg/m^2 and 30 kg/m^2 among Western populations.[3] Indeed, the current study supports the application of these lower thresholds for BMI and waist circumference among Asian Indians, although this point was not emphasized. Using the data supplied in table 1 of Das et al., the unadjusted odds ratios (ORs) for NAFL can be calculated for the various BMI categories relative to individuals with low BMI. Specifically, relative to persons with BMI $<$ 18.5 kg/m^2, the OR for NAFL $=$ 4.0 for individuals with BMI of 18.5-22.9 kg/m^2, OR $=$ 15.5 for BMI of 23-24.9 kg/m^2, and OR $=$ 20.2 for BMI $\geq$ 25.0 kg/m^2. Thus, what would be classified as normal BMI of 23-24.9 kg/m^2 imparted a risk of NAFL closer to that of BMI $\geq$ 25 kg/m^2, the standard BMI definition for overweight in the West.

The same factors associated with NAFL in other studies were identified in this study even though the population as a whole would not appear to be at risk for NAFL by Western standards. Relative to participants without NAFL, those with fatty liver had greater prevalence of abdominal obesity and diabetes; higher fasting plasma glucose, HOMA-IR (homeostasis model assessment of insulin resistance) score, and total cholesterol concentrations; and lower high-density lipoprotein cholesterol concentrations. These findings are in keeping with a metabolic study conducted in the United States of young, lean, healthy, sedentary, nonsmokers designed to contrast the metabolic profile of normal weight members of several ethnic groups, which found that individuals of Asian Indian descent had greater insulin resistance and greater hepatic triglyceride content.[4] Numerous studies have also demonstrated a high prevalence of type 2 diabetes and insulin resistance, as well as greater abdominal fat, among Asian Indians compared with other ethnic groups.[5,6]

Taken together, the results of the current study and studies of diabetes and metabolism among Asian Indians allow predictions regarding the frequency of NAFL among Asian Indians that extend well beyond the rural population study by Das and colleagues. In Asian Indian populations where insulin resistance, hyperglycemia, and visceral adiposity are common, NAFL may be expected to be prevalent. And because insulin resistance and hyperglycemia are more common among Asian Indians compared with other populations, it is anticipated that NAFL would also be common among persons of Asian Indian extraction. Thus, coupled with the inherent predilection that Asian Indians have toward insulin resistance and visceral adiposity, the rapid economic transition now occurring in India will usher in more Western alterations in dietary intake and lifestyle, which may be expected to put a large population of individuals at risk for the development of overt diabetes as well as NAFL.

What relevance does this study from West Bengal India have for the United States and other Western countries? According to the U.S. Census, approximately 2.5 million Asian Indians live in the United States and comprise one of the fastest growing ethnic groups.[7] Although the prevalence of diabetes has not been extensively studied among Asian Indians living in the United States, there is some evidence it is higher

than in most other ethnic groups in the United States.[8] Therefore, genetic and environmental settings are conducive for the development of NAFL among Asian Indians living in the United States and other industrialized countries, particularly as more Westernized lifestyles are adopted. For the purposes of risk stratification and metabolic and cardiovascular disease management, it is important to bear in mind that the thresholds for defining increased BMI and waist circumference for Asian Indians are lower than those for Westerners.

Beyond the hepatic manifestations of NASH, reliable determination of the full consequences of and public health burden imposed by NAFL will necessitate longer-term follow-up of prospective cohorts of individuals with NAFL. In the meantime, the accumulating evidence demonstrating the global prevalence of NAFL continues to call attention to the pervasive global epidemic of overweight and obesity, highlighting the urgent need for public health initiatives, along with basic and clinical research, aimed at limiting obesity and its consequences.

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