Editorial

Non-alcoholic Fatty Liver Disease: The Looming Epidemic

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Non-alcoholic fatty liver disease (NAFLD), a condition characterized by excess accumulation of fat in the liver occurring in people who consume little or no alcohol is emerging as the commonest liver disorder worldwide. The amount of excess fat deposited in liver in this condition usually exceeds by 5-10% of its weight [1]. Non-alcoholic fatty liver disease is a spectrum of clinicopathologic liver disease ranging from simple steatosis (SS) to non-alcoholic steatohepatitis (NASH) progressing to cirrhosis of liver and hepatocellular carcinoma (HCC) in few patients. NAFLD is considered as the hepatic manifestation of the metabolic syndrome as it shares a number of abnormalities including insulin resistance, visceral obesity, dyslipidemia, diabetes, high blood pressure, etc [2]. It is the foremost cause of elevated liver enzymes, after excluding common causes like hepatitis B, hepatitis C or alcohol [3]. Globally, the prevalence of NAFLD varies in the general population between 10-24%, with higher estimates (up to 74%) in those who are obese and in those from the developed countries. The prevalence is also increasing in developing countries, especially Asia, because of the changes in lifestyle, economic prosperity, and increasing prevalence of diabetes and obesity [4]

Estimates of the worldwide prevalence of NAFLD ranges from 6.3% to 33% with a median of 20% in the general population, based on a variety of assessment methods . The estimated prevalence of NASH is lower, ranging from 3 to 5%. The prevalence of NASH cirrhosis in the general population is not known.

Prevalence of NAFLD in High Risk Groups

Excessive BMI and visceral obesity are recognized risk factors for NAFLD. In patients with severe obesity undergoing bariatric surgery, the prevalence of NAFLD can exceed 90% and up to 5% of patients may have unsuspected cirrhosis [5] There is a very high prevalence of NAFLD in individuals with type 2 diabetes mellitus (T2DM). A number of studies from India have reported an ultrasonographic or histopathological presence of NAFLD ranging from 69% to 88% [6]. The prevalence of NAFLD in individuals with dyslipidemia attending lipid clinics was estimated to be 50% [7].

Two studies in this journal have addressed this emerging health epidemic of NAFLD in developing countries. They report a prevalence of NAFLD in patients with type 2 diabetes mellitus (T2DM), consistent with that observed in developed countries Pandharipande et al[8] report a prevalence of 62% in patients with T2DM whereas Somalwar [9] and Raut reported a prevalence of 56.66% in patients with T2DM in a population of patients attending two different government hospitals in Nagpur, India

Another close association of NAFLD is with metabolic syndrome (MS). Metabolic syndrome is characterized by the presence of Insulin Resistance (IR) in association with obesity, diabetes, dyslipidemia, and hypertension. Framingham heart study from the US showed that 63% patients with NAFLD have MS as compared to 25% of controls Indian data show a prevalence of MS in 50% of patients with NAFLD [10]. In another study, 88% of NASH patients had MS compared to 53% with simple steatosis. Moreover, MS was associated with high risk of severe disease like NASH or severe fibrosis. Pandharipande et al in the present issue also found an association of NAFLD with components of the metabolic syndrome. They also reported a higher prevalence of the various components of metabolic syndrome in patients with T2DM. MS was present in 61% of T2DM patients as compared to 32% in controls.

Clinical Presentation and natural history

The diagnosis of NAFLD requires the presence of hepatic steatosis and the absence of regular alcohol consumption of >20 g ethanol per day. A recent consensus meeting[11], concluded that, for NASH clinical trials candidate eligibility purposes, significant alcohol consumption be defined as >21 drinks per week in men and >14 drinks per week in women over a 2-year period prior to baseline liver histology (1 alcoholic drink is ~ 10 grams of alcohol per one drink unit).

NAFLD subjects can be asymptomatic. Symptoms if present are mostly nonspecific like general malaise, abdominal discomfort, vague right upper quadrant abdominal pain, nausea, and other nonspecific symptoms

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referred to the gastrointestinal tract. Rubbery/soft, hepatomegaly is common. More consistent features are obesity, diabetes, and hypertension. Small percentage of patients who present with NASH-related cirrhosis may present with ascites, splenomegaly, spider angiomas, palmar erythema, caput medusa or jaundice [12]

It is generally agreed that patients with simple steatosis have very slow, if any, histological progression, while patients with NASH can exhibit histological progression to cirrhosis. Twenty percent of patients with NAFLD progress to cirrhosis [13].

The long term outcomes of patients with NAFLD and NASH have been reported in several studies[14] Their findings can be summarized as follows; (a) patients with NAFLD have increased overall mortality compared to matched control populations, (b) the most common cause of death in patients with NAFLD, NAFL and NASH is cardiovascular disease, and (c) patients with NASH (but not NAFL) have an increased liver-related mortality rate.

Another piece of indirect evidence that supports the progressive nature of NASH is in the features of cryptogenic cirrhosis which is closely related to NAFLD.

Patients with cryptogenic cirrhosis have disproportionately high prevalence of metabolic risk factors (T2DM, obesity, metabolic syndrome) typical of patients with NAFLD, their liver biopsies frequently show one or more features of NASH, and studies have demonstrated the loss of histological features of NASH with the development of cirrhosis.

The most common reported cause of death in patients with NAFLD or NASH is cardiovascular disease. NAFLD is an independent risk factor for cardiovascular disease (CVD), after adjustment for traditional risk factors and components of the metabolic syndrome. Several epidemiological studies suggest that role of NAFLD is not limited as a marker of CVD, but indicates its active involvement in its pathogenesis. NAFLD involvement in developing whole body insulin resistance and atherogenic dyslipidemia along with the role of molecular mediators such as release of pro-atherogenic factors from the liver lead to progression of CVD. The marked increase in carotid artery intima-media thickness (IMT) is repeatedly demonstrated as reliable index of subclinical atherosclerosis in patients with NAFLD[15]. There is association between the histological severity of NAFLD and carotid IMT independent of classical risk factors, IR, and components of the MS NAFLD is associated with shorter life expectancy and CVD is the common cause of death in patients with NAFLD [16].

Somalwar and Raut, in this issue also report a higher prevalence of coronary artery disease in patients of T2DM with NAFLD as compared to those without NAFLD (70.58% vs. 21.11%, P<0.0001).

Given the potentially serious outcomes associated with NAFLD, especially NASH treatment strategies have to be evolved. The management of patients with NAFLD consists not only of managing obesity, hyperlipidemia, insulin resistance and T2DM, but also the evolving liver disease. Unfortunately, targeted pharmacologic management of NAFLD remains far from satisfactory. Therefore lifestyle changes such as diet modifications, exercise, weight reduction, and adequate management of T2DM together and independently, remain the only proven measures with some degree of success and should form the cornerstone of any treatment regimen. As patients with NAFLD without steatohepatitis have excellent prognosis and can be reversed with these modifications, specific treatments to improve liver pathology are needed in patients who have progressed to develop NASH. Insulin sensitizers like thiazolidinediones and antioxidants like vitamin E have a role in patients with biopsy-proven NASH but need further research to evaluate their beneficial impact.

The two studies in the present issue inform us that the problem of NAFLD is rising even in the relatively low socio economic strata of the populations that attend public hospitals and that clinics need to be equipped to prevent, diagnose and manage the large burden that is anticipated with the economic transition in India.

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