

Nonalcoholic Fatty Liver Disease: Time to Take the Bull by the Horns

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ABSTRACT

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in the world affecting almost one-fourth of the population. It may progress to nonalcoholic steatohepatitis (NASH), cirrhosis, end-stage liver disease, and liver cancer in the long run. Besides, it may make the natural history in other chronic liver diseases worse too. Furthermore, patients of NAFLD more often suffer from metabolic syndrome, ischemic heart disease, and extrahepatic malignancies than others, leading to a lower overall survival than the general population. Obesity and sedentary lifestyle are among the most important risk factors for NAFLD apart from increasing age, male sex, and certain genetic factors. Due to the rising incidence, possible adverse consequences, and the futile available treatment options, prevention is the key to tackle this health menace. Spreading awareness, adopting a healthy lifestyle with appropriate dietary modifications, regular physical activity are the cornerstones for challenging this unfolding monster.

Keywords: Awareness, Lifestyle change, Nonalcoholic fatty liver disease, Prevention.

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INTRODUCTION

Nonalcoholic fatty liver disease refers to a hepatic condition associated with fat accumulation in the liver exceeding 5% of hepatocytes in individuals who consume little alcohol.¹ Histologically, it encompasses a broad spectrum ranging from simple steatosis to NASH, which is virtually indistinguishable from alcoholic steatohepatitis,² NASH-related cirrhosis, end-stage liver disease, and even hepatocellular carcinoma.³

BURDEN

It would be euphemistic to describe the present scenario of NAFLD as an epidemic. What we really have today is a global pandemic, and we must get "Pandemic Ready" before it is too late. Various population-based studies have revealed the prevalence of NAFLD ranging from 30 to 40% in men and 15 to 20% in women in the West.⁴⁻⁶ On the contrary, the prevalence of NAFLD was found to be as high as 25% in rural predominant Indians.⁷ The global imaging-based prevalence of NAFLD too has been estimated to be around 25%.⁸ This indicates that a

population of around 1.8 billion individuals worldwide have this disorder! Moreover, with gradually increasing incidence, it has become the predominant cause of chronic liver disease in most nations of the world and is expected to be the leading indication for liver transplantation in the near future.⁹ However, a matter of great concern is that the global prevalence of NAFLD is still on the rise,¹⁰ which mandates the attention of medical practitioners, researchers, and both national and international policymakers.

NATURAL COURSE

There is considerable degree of uncertainty regarding the natural history and prognosis of NAFLD. This absence of uniformity is in part due to subtle individual differences in their genetics which modify their response to environmental factors and lifestyle leading to different disease phenotypes.¹¹ Progression of fibrosis in patients with simple steatosis is quite uncommon; on the contrary, NASH progresses more frequently to cirrhosis, end-stage liver disease, and hepatocellular carcinoma.^{5,12-14}

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However, few studies suggest that simple steatosis can evolve to NASH with advanced fibrosis, implying that it may not be a completely benign condition.¹⁴⁻¹⁶ Hence, due to the potential gap between our current understanding and pathophysiology of NAFLD, we are still unable to predict which subgroup of NAFLD will worsen earlier and that too when.

IMPLICATIONS

Long-standing NAFLD in a minority of patients can lead to NASH, and subsequently NASH-related cirrhosis, end-stage liver disease, and hepatocellular carcinoma.^{12,13} Besides, presence of NAFLD also increases the risk for fibrosis and aggravates the natural course in patients with other chronic liver diseases such as chronic hepatitis B¹⁷ and alcoholic liver disease.¹⁸ In the past, before the advent of directly acting antiviral agents, when pegylated interferon-alfa and ribavirin were the cornerstones of chronic hepatitis C therapy, presence of insulin resistance, which is an independent risk factor for NAFLD, was associated with poor sustained viral response.¹⁹ Besides, presence of NAFLD is frequently associated with several nonhepatic comorbidities. The most important and most frequently associated comorbidity is the metabolic syndrome or insulin resistance syndrome, and fatty liver was in fact considered as a hepatic manifestation of metabolic syndrome.^{20,21} However, recent studies favor the argument that the former is a better indicator for the latter than the existing criteria for metabolic syndrome.^{22,23} Furthermore, atherosclerotic cardiovascular diseases and extrahepatic malignancies of both gastrointestinal tract and other organs are also quite common in NAFLD, and surprisingly, they contribute more to the mortality in NAFLD than liver-related deaths.^{24,25}

RISK FACTORS

Risk Factors for NAFLD

Among the nonmodifiable risk factors, increasing age²⁶ and male sex⁵ are independent predictors. However, due to growing prevalence of obesity among younger age groups, NAFLD prevalence has increased considerably in children and adolescents.^{27,28} Besides, presence of certain endocrinological conditions like hypothyroidism²⁹ and hypogonadism³⁰ also predispose to NAFLD. In addition, related developments in the knowledge of genetics have identified the gene "patatin-like phospholipase domain-containing protein 3 (PNPLA3)" which is found to play a pivotal role in NAFLD.³¹

Among the modifiable risk factors, obesity is the most important risk factor according to most studies on NAFLD.³²⁻³⁴ The recent transition of nutrition in developing countries like India³⁵ has led to immensely high

incidence of NAFLD in the younger population,²⁸ which is a matter of great concern. Abdominal obesity, which is a marker of metabolic syndrome,³⁶ is currently considered as much more important than generalized obesity. Moreover, a direct association has been found between abdominal fat and liver fat.³⁷ Dietary factors like higher intake of meat, fat, spicy food, and fried food render an individual more susceptible to NAFLD.^{38,39} Besides, fast food^{39,40} and soft drinks⁴¹ that contain artificial sweeteners, such as fructose,⁴² are also strongly associated with NAFLD. On the contrary, there are certain foods which are beneficial in NAFLD. Coffee has favorable effect on liver enzymes,⁴³ fibrosis stage,⁴⁴ hepatocellular carcinoma,⁴⁵ and mortality in cirrhotic patients.⁴⁶ Besides, intake of diet rich in monounsaturated fatty acids and polyunsaturated fatty acids has been found to improve hepatic steatosis.⁴⁷ The low level of physical activity is also an important risk factor for NAFLD. The study from National Health and Nutrition Examination Survey (NHANES 2003–2004 and 2005–2006) have clearly demonstrated that NAFLD patients have low level of physical activity than the general population.⁴⁸ Subsequently, in a retrospective study on biopsy-proven NAFLD subjects of the Nonalcoholic Steatohepatitis Clinical Research Network (NASHCRN), data have shown that there is an inverse relationship between exercise intensity and severity of liver tissue injury in NAFLD patients.⁴⁹ This is of special significance in the context of counseling for NAFLD patients.

Prevention of NAFLD

As for any disease, awareness is the key and essentially the first step in prevention. Surprisingly, a large proportion of the general population remains unaware of this silent yet disconcerting disease.⁵⁰ Moreover, patient education programs are also lacking. In a recent study from Hong Kong, it was seen that 83% of the general population had never come across the term NAFLD.⁵¹ Another study from Italy which was conducted on general medical practitioners regarding their knowledge and practices on NAFLD revealed barely adequate awareness among the physicians, albeit significant improvements were observed following an educational intervention.⁵² Similarly, in a report from the USA, a significant proportion of primary care physicians were found to be unaware of guidelines on NAFLD.⁵³ Expectedly, a study from coastal eastern India revealed that despite a high NAFLD prevalence, a substantial proportion of patients with NAFLD were unaware about both NAFLD and obesity, especially the harmful effects of obesity. Paradoxically, two-fifths of the obese NAFLD patients felt that they were not obese.⁵⁴

The primary prevention of NAFLD will definitely require the elimination of the incumbent risk factors like central obesity, metabolic syndrome, and insulin resistance. The role of lifestyle modification as an effective treatment of diabetes mellitus has been shown in the Diabetes Prevention Program, which compared strict lifestyle modification (diet and exercise) with metformin and placebo in the prevention of diabetes.^{55,56} Adopting a healthier lifestyle can prevent development of NAFLD, like prevention of diabetes mellitus in high-risk groups. However, unlike diabetes, studies on prevention of NAFLD are scarce despite its high prevalence. In a study by Bae et al,⁵⁷ it was observed that regular exercise was associated with a reduced risk of having NAFLD. Furthermore, there is an inverse relationship between degree of cardiovascular fitness and incidence of NAFLD.⁵⁸⁻⁶⁰ Hence, a healthy lifestyle is essential for prevention of NAFLD, and this should include:

- Regular moderate-to-vigorous exercise for at least 60 minutes on at least 5 days a week⁶¹
- A balanced low-calorie diet with <30% fat⁶²
- Cutting down on fried food, spicy food,³⁹ meat, and soft drinks³⁸
- Avoidance of alcohol consumption^{39,63}

Statins,^{64,65} fenofibrate,^{66,67} and probiotics⁶⁸ have been tried as preventive strategies for NAFLD but further studies are needed to prove their role in prevention. Therefore, with no chemoprevention available, we are left with lifestyle changes as the only preventive modality for NAFLD, with awareness as the key.

It need not be overemphasized that the NAFLD menace can only be tackled by identifying the individuals at risk at a very young age and taking steps to address all the modifiable risk factors. A few small studies have demonstrated the relationship between childhood body weights with risk of adult NAFLD.⁶⁹⁻⁷¹ Further, a large prospective study also demonstrated that a gain in body mass index (BMI) between the ages of 7 and 13 years was positively associated with adult NAFLD after adjustment for initial as well as attained BMI.⁷² Hence, children and adolescents should be the targets for the awareness programs on NAFLD. Education about the importance of ideal dietary composition, regular physical activities, and concept of ideal BMI (<23)⁷ should be a part of school curriculum, if we are serious about taming this silent unfolding monster.⁷³

CONCLUSION

The last couple of decades have witnessed the rise of this silent killer named NAFLD. Despite a large risk of both liver-related and cardiovascular complications, we are yet to see an ideal noninvasive tool for severity assessment as

well as a safe and effective treatment. Hence, prevention is the only option to safeguard the future generation against this pandemic. Education, counseling, and lifestyle modification are the cornerstones of NAFLD prevention strategy. At the same time, we must be optimistic and put our efforts in serious research for development of an ideal treatment for NAFLD.

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