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Expert's Opinion

Non-Alcoholic Fatty Liver Disease in India: A Long Way to Go

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Introduction

In the past, non-alcoholic fatty liver disease (NAFLD) was considered to be a liver disease only with a spectrum ranging from non-alcoholic fatty liver (NAFL) to non-alcoholic steatohepatitis (NASH), which are considered as the most common risk factors for the development of liver cirrhosis and hepatocellular carcinoma (HCC).[1] But in the current scenario, NAFLD is recognized as a multisystem disease which is associated with metabolic conditions like obesity, type 2 diabetes (T2D), dyslipidaemia and also increasing not only liver disease-related morbidity and mortality, but also cardiovascular disease (CVD), chronic kidney disease (CKD), osteoporosis and extrahepatic malignancies.[2,3]

Non-Alcoholic Fatty Liver Disease Burden: Global and India

Globally, NAFLD has become the most common liver disease affecting almost 6-35% of world's population; but actual prevalence may be expected to be much higher than this. Its prevalence is widely variable depending on racial, genetic and dietary factors.[4] It is estimated that the prevalence in the Western population of NAFLD is higher than in Asian countries. But in various multiracial studies, it was observed that Asian-Indians have the paradox effect that is even at a lower body mass index (BMI) with central adiposity they are more susceptible to insulin resistance (IR) and thus to NAFLD.[4,5]

India is the country of variability in terms of race, diet, culture, genetic factors, etc. The rate of increase of type 2 diabetes mellitus (T2DM) in the country will soon make it the diabetes capital of the world with huge socio-economic and healthcare costs. Both insulin resistance and beta-cell dysfunction have a role to play in the pathogenesis. The reported prevalence of NAFLD in Indian population varies from 9% in rural to 32% in urban populations.[6] As per the Systolic Blood Pressure Intervention Trial (SPRINT), a population-based study, the prevalence of NAFLD ranges from 44% to 72%, across various regions of India. Prevalence was found to be lowest in the western part of India, while it was highest in northern states.[7]

What Should it be Called: Non-Alcoholic Fatty Liver Disease or Metabolic (Dysfunction) Associated Fatty Liver Disease?

In early the 1980s, the term NAFLD was coined for fatty liver without a history of significant alcohol intake. In the early part of 2020 however, the International panel consensus has proposed revision of the nomenclature of NAFLD to metabolic (dysfunction) associated fatty liver disease (MAFLD); considering its significant association with metabolic conditions like T2D, insulin resistance, obesity, dyslipidaemia, acute pancreatitis, etc. Actually, MAFLD is a previously recognized entity, as its relationship with T2D was observed by Beringer and Thaler in early 1970s, where-in they described the appearance of fatty liver in 75% individual with T2D and findings of liver cirrhosis in 2.6% versus 0.84% in the general population. This revised proposal has changed criteria to diagnose this condition; which now requires evidence of hepatic steatosis along with any one of the three features- obesity, T2DM and low/normal BMI with evidence of metabolic dysfunction. Changes in the nomenclature to MAFLD has added weight to the importance of insulin resistance and T2D in this condition, which demands the collaborative role of endocrinologist/physicians with hepatologist for appropriate management of this condition.[8]

Insulin Resistance - An Underlying Cause of Non-Alcoholic Fatty Liver Disease

NAFLD is a disease related to metabolic syndrome. IR pays a pivotal role in its pathogenesis and progression. IR is also a common soil for T2D and obesity; hence NAFLD is closely associated (70-80%) with these metabolic conditions.[9] Development of NASH is multifactorial, and IR has a key role as the initiator. As per the 2-hit hypothesis, the proposed explanation for the pathogenesis of NASH, IR is the first hit which leads to excessive fatty acids production in the circulation promoting the progressive changes from simple fatty liver to hepatic steatosis to NASH.[10] In the current era with no approved drugs available for NAFLD, oral antidiabetic drugs like metformin and pioglitazone are useful off-label agents to reduce IR in NAFLD subjects. More studies are required for the demonstration of the underlying mechanism of pathogenesis of NAFLD to develop effective agents for the prevention and treatment of NAFLD because of insulin resistance.

Non-Alcoholic Fatty Liver Disease and Dyslipidaemia – Elevation of Cardiovascular Risk

NAFLD carries an increased risk of liver failure as a result of cirrhosis. In addition, several other metabolic disturbances such as chronic inflammation, proatherogenic state, dysglyceamia, IR, and dyslipidaemia elevates the risk of CVD in NAFLD patients.[11] NAFLD is also associated with 2-3 times higher risk of dyslipidaemia, elevated coronary artery calcium (CAC) score and recurrent CV events. This overall implies that CVD is the leading cause of morbidity and mortality in NAFLD. The higher CV risk in NAFLD is due to derangement of lipoproteins, especially, high triglyceride-rich lipoproteins (TRL) in addition to increased liver fat and deranged conventional lipid profile. Statins and ezetimibe are the preferred options for dyslipidaemia in this setting which has shown to reduce CV events in some post hoc analysis.[11]

Challenges in Screening and Diagnosis of Non-Alcoholic Fatty Liver Disease

NAFLD is a condition wherein the majority of patients are asymptomatic in the initial stages. Currently, there are no consensus guidelines screening NAFLD at an early stage. Fatty liver is generally detected incidentally with other imaging tests and based on history/examination of the patient; a diagnosis of NAFLD can be entertained. Biopsy is the gold standard but is an invasive test and has other limitations. Biopsy is taken only from a small section of the liver (1/50,000th), whereas in steatosis, the extent of fat accumulation varies segment to segment and can even be focal, which may be difficult to evaluate through biopsy.[12] In this regard, multi-parametric magnetic resonance imaging is effective to evaluate the amount of intrahepatic fat and is widely used in clinical trials.[12] No diagnostic method however can differentiate between steatohepatitis and simple steatosis. Therefore, to prevent the progression of disease through early and aggressive treatment, it is of utmost importance to develop non-invasive biomarkers for identifying and staging NAFLD as also identifying those at risk of progression to end-stage liver disease at the earliest.[13]

Evaluation of co-morbidities associated with NAFLD is equally important; as it has a strong relationship with diabetes and metabolic syndrome, and is associated with increased risk of cardiovascular events because of increased atherogenic small dense low-density lipoprotein (sdLDL) particles, decreased large high density lipoprotein (HDL) particles and increased very-low-density lipoprotein (VLDL) or triglyceride-rich lipoprotein particles; which are responsible for development of atherosclerotic cardiovascular disease (ASCVD).[14]

Challenges in the Treatment of Non-Alcoholic Fatty Liver Disease

From the management point of view, weight loss-based lifestyle modification has a key role in prevention/progression of NAFLD. Yoshioka N *et al*. observed that NAFLD remission rates reached a plateau of 44% in subjects with 2% per year weight loss, while ≥7% weight loss also improved histological disease activity in NASH.[15] However, only diet and exercise regimens may not be able to achieve and/or maintain a 10% weight loss.

Asian and international guidelines have a different viewpoint on the pharmacological approach to treat NAFLD. The EASLD, AASLD and Asia-Pacific guidelines recommend pharmacological approach only for patients with NASH and fibrosis, while the NICE guideline proposes therapy for subjects with an advanced liver fibrosis score (ELF test >10.51). Some international authorities like the AISF recommend starting drug therapy in patients with high risk for disease progression also. The present guidelines are not in line for the management/pharmacological therapy of NAFLD.[16-18]

For the pharmacological management of NAFLD, metformin, pioglitazone, vitamin E, obeticholic Acid, glucagon-like peptide-1 (GLP-1) analogues, sodium-glucose cotransporter 2 (SGLT2) inhibitors and dual peroxisome proliferator-activated receptor (PPAR) agonist are commonly used medications, but they have not been approved in most of the countries. A lot of therapies targeting de novo lipogenesis, fat deposition, oxidative stress, inflammation, apoptosis and liver fibrosis are under investigation.

All guidelines recommend that the use of these medications is off-label and that the decision should be discussed with the patient, carefully balancing the benefit/risk ratio.[19] In the early 2020s, the Drug Controller General of India (DCGI) has approved saroglitazar (dual PPAR α/γ agonist) for the management of NASH/NAFLD in India, the first approved drug by any country in the world. But its real-world experience is yet to be shared by clinicians.[20]

Bariatric surgery is an option for reduction of weight and metabolic complications, in a specific category of patients who are unresponsive to lifestyle changes and pharmacotherapy.[21] For end-stage liver disease, liver transplantation is the only option, but the high cost and availability of resources limit this approach.[22]

Need to Improve Awareness and Education About Non-Alcoholic Fatty Liver Disease

Currently, one of the biggest challenges is to increase awareness and educate the general population about NAFLD. As per the Coronary Artery Risk Development in Young Adults (CARDIA) study from the USA, out of 700 participants (approx.), only 2.4% with computer tomography (CT)-defined NAFLD were aware of a diagnosis of NAFLD.[23] In one Asian community-based study, it was observed that perception about the disease is very low. 75% of the population with one or more metabolic risk factors were not even aware of their high risk for NAFLD.[24] The low awareness level, highlights an opportunity to increase public as also physician-level education regarding NAFLD with the goal of early diagnosis as also implementing early treatment strategies.

Conclusion

With the increase in the prevalence of T2DM and alarming increasing obesity in children as also adults the prevalence of NAFLD is going to increase. Thus, there is an urgent need for an appropriate guideline-based management strategy for early screening, diagnosis and treatment to achieve better outcomes. This needs a collaborative approach of clinicians, healthcare agencies, regulatory authorities and international societies to formulate region-specific guidelines. Several drugs targeting various pathogenetic pathways are in the pipeline, and we hope to see positive results of the trials very soon.

Declaration of conflicting interests

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