View Point

Non-alcohlic Fatty Liver Disease (NAFLD): Is it a Dormant Volcano or Tip of an Iceberg?

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Abstract

Non-alcoholic fatty liver disease (NAFLD), a major cause of chronic liver disease, is known to affect a quarter of the global adults. Natural history of NAFLD shows interindividual variation, traditionally it progresses from simple steatosis to steatohepatitis to fibrosis/cirrhosis and finally yet rarely to hepatocellular carcinoma. It is largely a lifestyle-related disease and is often labeled as the hepatic manifestation of metabolic syndrome. Both prevention and control of NAFLD include controlling risk factors (obesity, diabetes mellitus, hypertension and dyslipidemia), through lifestyle modification and medications. Drug therapy for NAFLD *per se* is still evolving and till date, no drugs are approved. It is clinically silent, especially in the early stages, and is a diagnosis of exclusion. Certain easily calculated indices can stratify cases into high or low risk for advanced fibrosis, thereby dictating appropriate monitoring and treatment measures. In addition to complications specific to liver disease in those who do progress to advanced fibrosis or cirrhosis, an increased risk of nonliver disease-related morbidity and mortality is also present. Challenges are manifold and include rising burden due to ever-growing epidemic of diabetes and obesity, low public awareness, fragmented healthcare, no approved drugs, and dearth of data on magnitude and epidemiology of the disease. The recent integration of NAFLD into the National Program for Prevention and Control of Non-Communicable Diseases (NPCDCS) by the Ministry of Health and Family Welfare of India is a welcome step in this direction as the contributory factors are mostly the same for all diseases and controlling any one or all of them will have a desired impact on the prevalence of all the diseases under this program.

Keywords: Liver fibrosis, National Program for Prevention and Control of Non-Communicable Diseases, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, obesity

Introduction

Non-Alcoholic Fatty Liver Disease (NAFLD) is characterized by the abnormal accumulation of ≥ 5% fat in the liver in the absence of secondary causes, such as harmful alcohol use, viral hepatitis, or medications.[1,2] It is actually a spectrum of lesions in the liver ranging from fatty liver to non-alcohlic steatohepatitis (NASH) that may lead to advanced fibrosis, cirrhosis, rarely hepatocellular carcinoma, and ultimately death. Roughly one-fifth progress from fatty liver to NASH and further fifth go on to develop cirrhosis.[3]

NAFLD is mushrooming at a dramatic rate globally and especially in the developing world, reflecting an increase in the incidence of type 2 diabetes mellitus and obesity. American Association for the Study of Liver Diseases (AASLD) has considered NAFLD and NASH as having "previously exclusionary, negative and confounder terms that used potentially stigmatizing language." In June 2023, it announced a better term for NAFLD- metabolic dysfunction-associated steatotic liver disease (MASLD); likewise, NASH has been better termed as metabolic dysfunction-associated steatohepatitis (MASH).[4]

MASLD, commonly referred to as NAFLD encompasses patients with liver steatosis (identified on imaging and/or biopsy) having at least one of the following risk factors.[4] (after ruling out other causes of steatosis):

1. BMI ≥25 kg/m^2 or WC >90 cm (M), 80 cm (F) (ethnicity adjusted)

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2. Fasting serum glucose ≥100 mg/dL or 2-hour postload glucose levels ≥140 mg/dL or HbA1c ≥5.7% or type 2 diabetes mellitus or treatment for type 2 diabetes mellitus
3. Blood pressure ≥130/85 mmHg or on antihypertensive therapy,
4. Plasma triglycerides ≥150 mg/dL or on lipid-lowering therapy,
5. Plasma HDL-cholesterol ≤40 mg/dL (M) and ≤50 mg/dL (F) or on lipid-lowering therapy.

Global prevalence of NAFLD is around 30%.[5] A meta-analysis (1990-2019)[6] also estimated its prevalence as being around 30%.

India has a paucity of data in this regard. A meta-analysis (50 studies)[7] gave a pooled prevalence of NAFLD in adults as 38.6% (95% CI 32–45.5); separately it was 28.1% (95% CI 20.8–36) and 52.8% (95% CI 46.5–59.1) in average-risk and high-risk subgroups respectively. Estimated NAFLD prevalence was obviously higher in hospital-based data (40.8%). In the same analysis, prevalence among non-obese and obese children was 12.4% and 63.4% respectively.[7] It further highlighted that community-based studies are few and also rural areas are underrepresented.

NAFLD remains largely unidentified and underreported due to general unawareness, silent nature (mostly diagnosed incidentally), and to an extent "indifferent attitude of physicians." Owing to lack of effective medications against NAFLD and ever-growing epidemic of obesity, the burden is bound to increase in the future.

Etiopathogenesis

It has a multifactorial etiology and risk factors include advanced age, presence of type 2 diabetes mellitus (≥ 50% of patients with type 2 diabetes mellitus have NAFLD[8]), obesity (truncal or android type), metabolic syndrome, dyslipidemia, hypertension, polycystic ovarian syndrome, insulin resistance, and obstructive sleep apnea. Their presence is also associated with a greater risk of progression to NASH and advanced fibrosis. Emerging associations are found with hypogonadism, osteoporosis, hypopituitarism, hypothyroidism, and psoriasis.[9] Smoking and air pollution (prolonged exposure to PM2.5) are other important risk factors for NAFLD progression.[8] Deposition of visceral adipose tissue (more prevalent in Asians), is of significance as compared to subcutaneous tissue.[9] Food rich in sugar or fat or excess calories further contributes, and so does the sedentarism due to a rise in desk jobs. A synergistic effect can be seen when these factors coexist with significant alcohol consumption. Exercise and coffee seem to be protective.[9] In addition to the above, studies have also demonstrated a higher risk of NAFLD in first-degree relatives compared with the general population suggesting a genetic predisposition to the disease.[8] Identification of associated genes may be important in the future to help in risk stratification and offering gene therapy. Advancing age (especially after the 5th decade) linked with a higher risk is probably because of increased duration of disease. Influence of gender is not clear (although more prevalent in females, but more adverse phenotype in males).[8] The gut microbiome has a role to play in the occurrence of NAFLD as well as its progression to NASH by altering hepatic carbohydrate and lipid metabolism and tipping the balance of pro and anti-inflammatory signals in the liver.[10] As per the original "two-hit hypothesis," liver fat deposition is the first hit-increasing insulin resistance and making the liver vulnerable to a variety of cellular and molecular changes. The second hits include oxidative stress by reactive oxygen species, lipid peroxidation, release of pro-inflammatory cytokines and gut bacterial endotoxins and cause cellular necrosis and apoptosis.[11] These may bring about collagen deposition and fibrogenesis. The resultant scar formation and cirrhosis state can serve as a nidus for malignant transformation into a hepatocellular carcinoma.[1]

Clinical features

Field-based early detection of NAFLD is challenging. An Indian community-based study among rural adults[12] observed that NAFLD often has no early symptoms (fat belly could be one signal). When diabetes, high cholesterol/triglycerides, or heart problems accompany the disease, patients may have symptoms related with these co-morbidities. As fatty liver disease worsens, vague symptoms of chronic fatigue or weakness also appear. Same has been observed by another review study[11] where majority cases were asymptomatic and only few experienced fatigue, right upper quadrant discomfort, hepatomegaly, acanthosis nigricans, etc. Only very few presented with end-stage liver disease (liver failure).

Diagnosis: It requires demonstration of hepatic steatosis either by radiology/histology with exclusion of secondary causes of fat deposition such as alcohol consumption, prolonged use of drugs (corticosteroids, tamoxifen, methotrexate and amiodarone), hepatitis C virus infection, Wilson's disease, autoimmune hepatitis, severe malnutrition, etc. It is most often identified through incidental findings of raised liver enzymes-alanine transaminase (ALT) more commonly than aspartate transaminase (AST); however, the degree of elevation does not correlate with the severity of disease. Serum alkaline phosphatase may also increase to 2-3 times the upper limit of normal in some cases.[11]

Few calculated scores using simple inexpensive clinical parameters can help with providing diagnostic and prognostic information such as:

1. NAFLD fibrosis score (NFS) to indicate progression of fibrosis: components include age, body mass index (BMI), AST, ALT, platelets, albumin, and hyperglycemia.
2. Fibrosis-4 (FIB-4) index: components include age, AST, ALT, and platelets.
3. Aspartate aminotransferase to platelet ratio index (APRI)
4. BARD score: components include BMI, AST, ALT, and type 2 DM.

These have fairly good negative predictive but poor positive predictive value especially at extreme of ages. Search for

an ideal biomarker for NASH is on and hopefully consortia such as US-based NIMBLE (NonInvasive Biomarkers of Metabolic Liver Disease) and Europe-based LITMUS (Liver Investigation: Testing Marker Utility in Steatohepatitis), will furnish some information in the future.[9]

Radiology: These are noninvasive in nature and include fibro scan, ultrasonography, computerized tomography, magnetic resonance elastography, and MRI-derived proton density fat fraction (MRI-PDFF). MRI-PDFF being the gold standard imaging technique is additionally accurate in detecting dynamic change as a response to therapy. However, because of cost and time consumption, it is used only in the context of clinical trials.[9]

USG: It is cheap, radiation-free and relatively easily available. This test has a good accuracy only when more than 20-30% of hepatocytes are steatotic. Also, it is subjective and less accurate to detect early disease.[13]

Liver biopsy: It remains the gold standard for diagnosis and characterizing the histologic alterations and is considered in patients with NAFLD who are at increased risk of progression to NASH and fibrosis and those with suspected NAFLD where presence/severity of other coexistent chronic liver diseases cannot be ruled out. Grade (degree of necro-inflammatory activity) and stage (location and extent of abnormal collagen deposition) are separate features and assessed and mentioned accordingly.[14]

Fatty liver is devoid of any evidence of hepatocellular injury whereas steatohepatitis has inflammation of hepatic lobules and hepatocellular ballooning independent of presence or absence of cirrhosis.

NAFLD activity score (NAS) quantifies disease activity; and includes three components with minimum and maximum scores namely steatosis (0-3), lobular inflammation (0-3), and hepatocyte ballooning (0-2). A score of ≥5 is diagnostic of NASH. The disadvantage is that fibrosis stage is not included in this score and that it cannot be used for monitoring response to therapy.[9]

Biopsy has its drawbacks in the form of invasive nature causing morbidity, rarely, mortality in addition to expense, sampling error-lack of representativeness, need of expert interpretation, and considerable interobserver variability.[9]

Attempts have been made to use simple anthropometric indicators such as body mass index (BMI), waist circumference and height ratio (WHtR), in the population with type 2 diabetes mellitus to detect NAFLD cases at an early stage.[15] However so far, the yield of cases is not impressive as these indicators have poor positive and negative predictive values.

Management

Till date, no specific drug therapy has been proved to be efficacious in NAFLD, therefore, most central to effective management is lifestyle modification targeting weight loss achieved by dietary modification and regular physical exercise. Also, diabetic control, hypertension, and dyslipidemia should be addressed. Smoking and alcohol cessation are equally important.

Figure 1 depicts the clinical care pathway for the risk stratification and management of patients with non-alcohlic fatty liver disease.

Diet: A high fiber intake, with a reduced intake of carbohydrates (sugars and refined carbohydrates), is recommended. A healthy eating pattern based on seasonal fruits, pulses, beans, nuts, oil rich in monounsaturated fatty acids, vegetables, whole grains, and fish with moderate intake of low-fat dairy products, poultry, and eggs may be adopted. Prolonged intake of sugary drinks, sweets, processed meat, and red meat should be avoided.[17] Caffeine (at least 2 cups/day) and vitamin E (800 IU/day) both being antioxidants provide some hepatoprotective benefit.[11]

Weight loss: Significant weight loss (7-10%) can bring about remission of NAFLD/NASH and to an extent even regression of fibrosis.[18] This can be achieved by maintaining a daily calorie deficit of about 500-1000 Kcal or reduction of 30%.[17] Bariatric and metabolic surgeries can help those with BMI > 35 (32.5 in Asians) with comorbidities (type 2 DM, pre-DM, uncontrolled hypertension) as it has been found to effectively resolve NASH or NAFLD in the majority of patients without cirrhosis.[11]

Exercise: Physical aerobic exercise reduces visceral fat effectively, including the intrahepatic triglyceride content.[18] As per the EASL guidelines,[17] 150-200 minutes/week of moderate-intensity aerobic exercise and resistance training is recommended. Benefits are accrued in the markers of liver injury even in the absence of weight loss.

Drugs: As mentioned earlier, currently there are no medications available for NAFLD, but drugs used for associated comorbidities as per the clinical setting can potentially benefit in NAFLD. However, no consistent antifibrotic effect has been demonstrated.

Glitazones such as pioglitazone (30-45 mg daily) may be used in biopsy proven NASH patients with coexistent diabetes mellitus. Vitamin E (800 IU daily) could help in select nondiabetics with biopsy proven NASH. Certain other drugs which are being tried include GLP-1 agonists, SGLT-2 inhibitors, pentoxifylline, and obeticholic acid however, their therapeutic impact needs to be defined.

As of now, India is the only country where a specific pharmacotherapy has been approved by a national regulatory agency (Drug Controller General of India or DCGI)) for the management of NASH-Saroglitazar (dual PPAR alpha/gamma agonist) in the dose of 4 mg/day.[19]

In patients with stage F4 (cirrhosis), liver transplantation remains an option. For hepatocellular carcinoma, a combination of resection, radiotherapy, chemotherapy (e.g. sorafenib), and liver transplantation may be required.

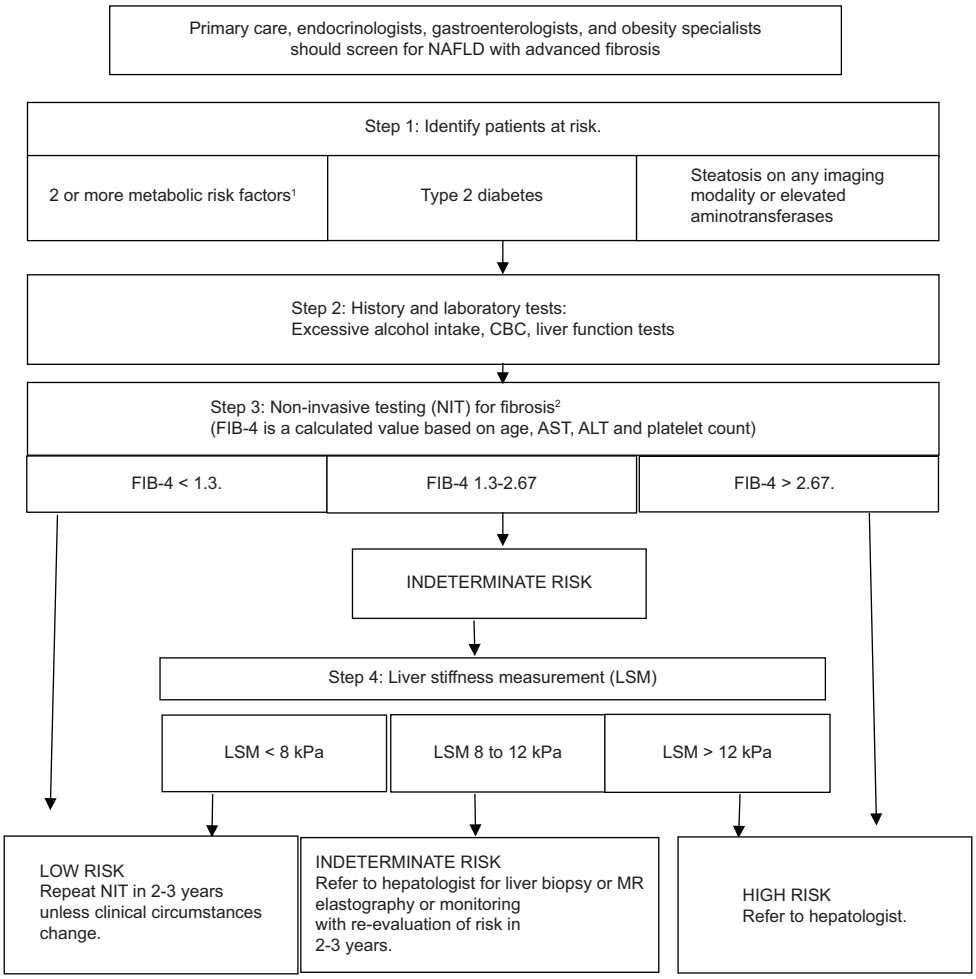

Figure 1: Clinical care pathway for risk stratification and management of patients with non-alcoholic fatty liver disease. (Adapted from[16]). [1]Metabolic risk factors: central obesity, high triglycerides, low HDL cholesterol, hypertension, prediabetes or insulin resistance. [2]For patients 65+, use FIB-4 <2.0 as the lower cutoff. Higher cut-off does not change

Complications

Commonest cause of death is cardiovascular disease (not liver disease), mostly due to endothelial vascular dysfunction, atherogenic dyslipidemia, and myocardial remodeling.[9] NAFLD cases have higher occurrence of unstable angina, myocardial infarction, heart failure, sudden death, transient ischemic attack, stroke, and malignancies, especially hepatic and colon. A meta-analysis found a 2-fold increased risk of type 2 DM in patients with NAFLD.[20]

Complications specific to advanced liver disease such as ascites, hepatic encephalopathy, variceal hemorrhage, and hepatocellular carcinoma are common in patients who progress to cirrhosis.[21]

Public health initiatives

Rightly, the Government of India has launched operational guidelines for the integration of NAFLD into the existing National Program for Prevention and Control of Non-Communicable Diseases (NPCDCS) in the year 2021.[22] In fact, India is the first country to include NAFLD in one of its national programs. The implementation (managing co-morbidities such as obesity, type 2 diabetes, and hypertension and tackling risk factors through diet and lifestyle measures) at field level will be very cost-effective as the risk factors of NAFLD are common with other chronic noncommunicable illnesses under the NPCDCS. Furthermore, in May 2023, the ministry of Health and Family Welfare has decided to rename the program from NPCDCS to National Program for Prevention and Control of Non-Communicable Diseases (NP-NCD).

NAFLD is designed and included within the broad structure as laid out in Figure 2 at each level of healthcare delivery system.

Role of medical colleges: There are more than 700 medical colleges in India and they can play an important role in the fight against NAFLD as they are instrumental in providing (1) quality medical care to the community, (2) training health care providers and (3) generating evidence through multi-disciplinary researches to provide inputs in policy decisions.[2] To begin with, the teaching curricula of doctors and nursing professionals should include the competencies about the prevention and control of various noncommunicable diseases (NCDs) including NAFLD.

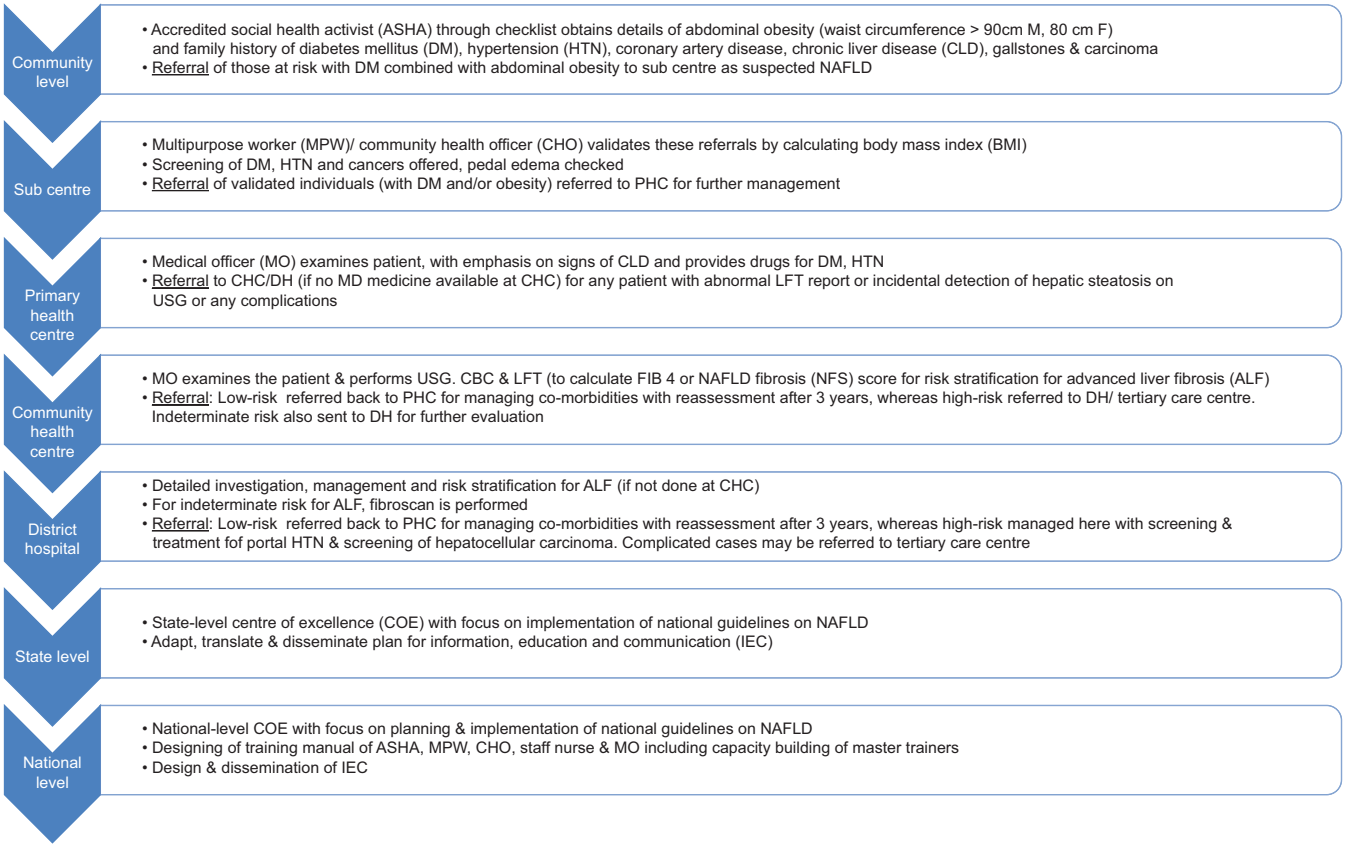

Figure 2: Operational structure for the integration of NAFLD under NPCDCS at different levels of health care delivery (Adapted from[22])

Health promotion is key strategy to tackle this silent epidemic of NAFLD. Various risk factors like overweight/obesity, physical inactivity, smoking, and alcohol drinking are common in young people; same group of individuals is also targeted by companies advertising unhealthy food, tobacco/alcohol, etc. Hence, engaging youth at school, college, and workplace in fight against NAFLD is critical. Health promotion strategies can be integrated in ongoing school health program which is supported by medical colleges in their respective field practice area. Medical colleges can train teachers and students and engage them through street plays, debates, and health talks.

Challenges: Large-scale multi-centric community surveys in rural/urban areas are must to know the exact magnitude of problem which can draw the attention of program managers to plan activities. In view of the nonavailability of a clear-cut field-based screening or diagnostic criteria of NAFLD, community-based surveys are difficult to undertake. Despite its high prevalence in adults and children, NAFLD remains a grossly under-appreciated disease because of the poor awareness in the community and care providers. Fragmented healthcare and social inequity especially in countries such as ours that are seeing the upsurge in cases further compound the issue. In view of no approved drug therapy, prevention is the only effective tool and dietary/lifestyle modifications remain the first line, which are in fact difficult to implement. Studies are also needed to know the magnitude of disease in different subgroups/areas and also to understand its epidemiology in the sense that what proportion of NAFLD cases progress to NASH or to other late complications.

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Conflicts of interest

There are no conflicts of interest.

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