Non-alcoholic fatty liver disease - Clinician's perspective

Sagar Shankar Patil[1], Shrikant V Mukewar[2]

ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) is rapidly becoming the common cause of liver disease among Indian population. It is a hepatic manifestation of metabolic syndrome NAFLD involves wide spectrum of disease with potential severity ranging from fibrosis, cirrhosis and hepatocellular carcinoma. Therefore it is important to have concise protocol to diagnose and manage it to avoid future complications. Lifestyle modification including healthy diet and exercise for weight loss are mainstay of NAFLD treatment. Pharmacotherapy or surgical approaches are often required in view of low patient compliance Most of NAFLD patients are screened and can be well managed by primary physician NAFLD patients with advanced liver fibrosis or with high risk should be referred to specialist for further care

Introduction :

Non-alcoholic fatty liver disease (NAFLD) is rapidly evolving, as a common cause of liver disease in the Indian population[1]. It is a commonly faced scenario in clinical practice. Overall, patients with NAFLD have a 34% to 69% increased chance of dying with hepatic and non-hepatic complication over 15 years in comparison with the general population. Hence, a concise protocol for the diagnosis and management of NAFLD is quintessential to avoid future complications including cirrhosis and hepatocellular carcinoma (HCC).

What is NAFLD?

NAFLD is characterized by excessive hepatic fat accumulation and is associated with insulin resistance (IR). It is defined by the presence of steatosis in > 5% of hepatocytes according to histological analysis[2]. NAFLD include two pathologically distinct conditions : non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH). In NAFL, hepatic steatosis is present without evidence of significant inflammation or any evidence of fibrosis, which represents the more benign end of the disease spectrum. In contrast, NASH involves a wide spectrum of disease with severity ranging from fibrosis to cirrhosis and hepatocellular carcinoma. 1 in 5 people with NAFLD have NASH on liver biopsies. The diagnosis of NAFLD requires the exclusion of secondary causes like medications, hepatitis C, starvation, parenteral nutrition and significant alcohol consumption (< 30 grams / day for men and < 20 grams / day for women)[2].

[1]Consutant Gastroenterologist, Nagpur
[2]Director of Midas Multispeciality Hospital,Nagpur

Address for Correspondence -
Dr. Sagar Shankar Patil
E-mail : sagrock_03@yahoo.com

How common is NAFLD in clinical practice?

Nonalcoholic fatty liver disease (NAFLD) is considered to be common cause of chronic liver disease in both the developed as well as developing countries. NAFLD is a hepatic manifestation of metabolic syndrome. The major risk factors for NAFLD are central obesity, type 2 diabetes mellitus, dyslipidemia, metabolic syndrome and age more than 50 years. Notably, NAFLD does not only affect the obese population but also has been demonstrated among nearly 20% of non-obese 'healthy' Asians[3]. Various Indian studies have shown prevalence of NAFLD is ranging between 15-30%, which is comparable with western population[4].

How to diagnose NAFLD in clinical practice?

Fatty liver is a common incidental finding seen on imaging during clinical practice. Most of the patients are asymptomatic; some patients may complain of fatigue, malaise and vague right upper abdominal discomfort. They may have hepatomegaly on physical examination. Early diagnosis is possible if a high index of suspicionis

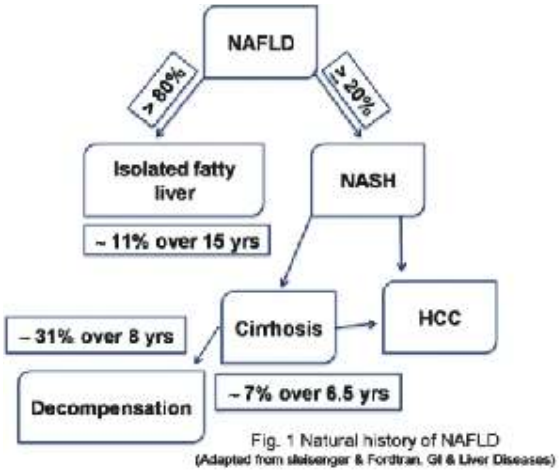

Fig. 1 Natural history of NAFLD
(Adapted from sleisenger & Fordtran. GI & Liver Diseases)

maintained in those with risk factors for metabolic syndrome. It should be suspected in patients with unexplained elevation of transaminases (AST/ALT), which is seen in 20-30% of patients and in patients with unexplained cause of cirrhosis, or in patients previously diagnosed as cryptogenic cirrhosis.

Imaging

Ultrasonography is the preferred first line screening procedure, as it is simple, non-invasive, inexpensive and easily available. It has a sensitivity of 60-90% while specificity of 65-95%. USG has limited sensitivity and does not reliably detect steatosis. If present less than 20% or in individuals with high body mass index (BMI) > 40 kg / m 25. Other imaging modalities like non-contrast CT scan and MR imaging provides an accurate and rapid assessment of hepatic steatosis. However availability and high cost is an issue. Findings in patients with NAFLD include increased echogenicity on ultrasound, decreased hepatic attenuation on computed tomography or an increased fat signal on magnetic resonance imaging.

Table 1 : **Comprehensive evaluation of suspected NAFLD patients**

1)	Rule out significant alcohol intake : < 20 g / day (women), < 30 g / day (men)
2)	Personal and family history of diabetes, hypertension and cardio vascular disorder
3)	Physical assessment of obesity and metabolic syndrome like BMI, waist circumference, change in body weight
4)	Serological investigation like Hepatitis B/Hepatitis C virus infection considering common etiology of liver disease.
5)	History of steatosis - associated drugs like Amiodarone, antiepileptic like valproate, antiretroviral medication.
6)	Biochemical testst to assess liver function and metabolic syndrome: serum bilirubin, transaminase levels, Gamma GT, albumin, globulin, fasting sugar, HbA1c, OGTT, fasting insulin [HOMA-IR]) and fasting lipid profile
7)	Hematological tests : Complete blood count including total platelet count. A low platelet favors significant fibrosis or cirrhosis.

Role of Non invasive test in NAFLD

Fibrosis is the most important prognostic factor in NAFLD and is correlated with liver-related outcomes and mortality[6]. Advanced fibrosis, as determined by non-invasive serum biomarker, has been shown to predict liver-related complications and mortality.

Various biomarkers and scores of fibrosis, as well as elastography are acceptable non-invasive procedures for the identification of cases at low risk of advanced fibrosis. Non-invasive markers should be directed to identify the risk of NAFLD among individuals with metabolic syndrome. It is useful to monitor disease progression and to predict response to therapeutic interventions.

NAFLD fibrosis score is one of the best-validated clinical algorithm which is available online. It has high positive predictive value. Presently mentioned scores reliably predict the presence but not the severity of steatosis.[8]

Role of Elastography

Elastography measures the stiffness of the liver. Stiffness depends on the amount of scaring in the liver. Shear wave elastography (SWE) is most

Table 2 : **Panels of indirect markers of hepatic fibrosis**[7]

Test	Components of the panel	Cutoff	PPV	NPV	Sen	Sp
Clinical calculators						
FIB-4	AST, ALT, age, platelet count	1.3	59	88	74	78
BARD	AST/ALT, BMI, age	2.0	41	90	89	44
APRI	AST, platelets	1.0	51	49	27	89
NFS	AST/ALT, IFG/DM, age, BMI, platelets, and albumin	-1.5	44	86	78	58
Proprietary panels of indirect markers						
NAFLD Fibrometer	AST, ALT< weight, age, platelets, glucose and ferritin	0.8	89	91	79	96
Fibrotest	Age, sex, bilirubin, GGT, haptoglobin, apolipoprotein A1, and a2-microglobulin	0.7	76	73	15	98

Abbreviations : PPV - Positive predictive value, NPV - Negative predictive value, Sen - Sensitivity, SP - Specificity,

widely studied. SWE in turn can be classified into Transient Elastography (TE) or acoustic radiation force imaging (ARFI). In TE, the force is a physical force used to displace the tissue, whereas in ARFI, a radiation force is used to generate the shear force.

Transient elastography is an ultrasound - based technology to measure liver stiffness. It has a short procedure time (< 5 min) and results are obtained immediately. It can be done at the bedside or in an outpatient clinic. It has a ability to detect advanced fibrosis (cut off values - 11 &17kPa) with sensitivity and specificity of 94% and 95% respectively[9]. It can also monitor severity of hepatic fibrosis in NAFLD patients. TE is a reliable method for the diagnosis of cirrhosis in patients with chronic liver diseases, that generally performs better at ruling out rather than ruling in cirrhosis (negative predictive value higher than 90%). In ARFI, radiation force is used to generate the shear force. ARFI is referred to as point-SWE if measurements are made from one area (0.5 cm 1.0 cm) or 2-dimensional - SWE if multiple points are measured sequentially.

Screening of liver fibrosis by both serum markers and elastography is recommended by EASL guidelines particularly among patients with metabolic syndrome or type 2 diabetes mellitus who have higher risk of liver fibrosis.

When to consider liver biopsy?

Liver biopsy remains the gold standard for definitive diagnosis of NASH as well as evaluation of the degree of inflammation and stage of fibrosis. Although not all patients with NAFLD need to undergo liver biopsy, it should be considered for

Table 3 : **Elastography**

TE	ARFI
Shear force is mechanical.	Shear force is acoustic.
For detecting F2 or greater fibrosis : ● Sensitivity was 0.78 (95% CI: 0.720.83). ● Specificity was 0.84 (95% CI: 0.750.90).	For detecting F2 or greater fibrosis : ● Sensitivity was 0.74 (95% CI: 0.660.80). ● Specificity was 0.83 (95% CI: 0.750.89).
Pressure is reported in kPa.	Shear wave speed reported in m/s.
It cannot be used in patients with ascites.	It can be used in patients with ascites

patients with high suspicious of chronic liver disease or those with persistently elevated transaminase levels. Liver biopsy features included steatosis, hepatocyte ballooning and lobularinflammation[10]

The diagnosis of nonalcoholic fatty liver disease (NAFLD) requires all of the following :

- **Demonstration of hepatic steatosis by imaging or biopsy**
- **Exclusion of significant alcohol consumption**
- **Exclusion of other causes of hepatic steatosis**

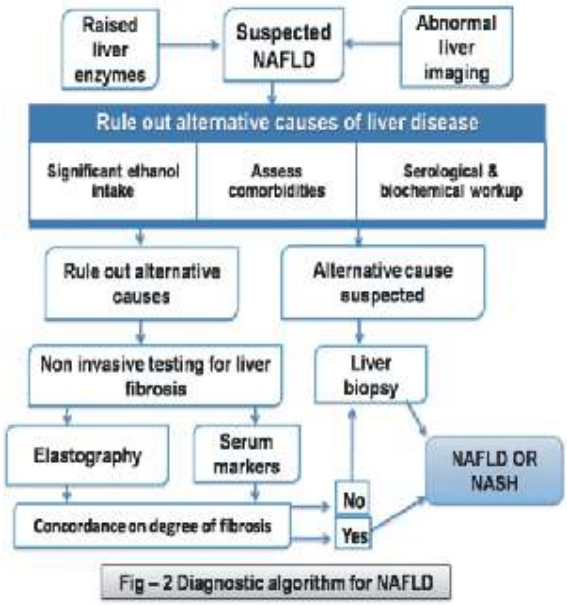

Fig – 2 Diagnostic algorithm for NAFLD

How should NAFLD be managed in my clinical practice?

A : Role of diet and lifestyle change

A structured program aimed at lifestyle changes has proven to be beneficial in NAFLD. Lifestyle modifications including weight loss, dietary changes and physical exercise should be the first-line treatment for NAFLD patients. Histological improvement is directly associated with magnitude of weight loss. About 3% - 5% of body weight loss can improve steatosis and up to 10% can improve necro-inflammation[11]. Patients without NASH or fibrosis should only receive counseling for healthy diet and physical activity without any pharmacotherapy. Dietary recommendations should consider energy restriction and exclusion of NAFLD - promoting components like processed food and beverages high in added fructose such as soft drinks. Coffee (ideally, without sugar) may be considered as an adjunct in NAFLD as it is associated with improved outcomes in various studies[12]. Clinicians should encourage healthy diet like higher consumption of fiber and antioxidant-rich fruits and vegetables as well as lower consumption of saturated fat. Exercise has resulted in reducing visceral fat, improving insulin sensitivity and maintaining weight loss, which in turn helps in reducing steatosis as well as treating metabolic syndrome both[13]. Energy restriction is advocated with 500-1000 kcal energy defect to induce weight loss of 500-1000 gm.

7-10% of total body weight should be the target. Long-term maintenance approach, combining physical activity according the principle of cognitive-behavioral treatment is advocated as per EASL guideline. Weight reduction effectively normalizes levels of liver enzymes and insulin resistance.

B : Role of pharmacotherapy

Although dietary intervention and exercise remain the first-line therapy, pharmacotherapy or surgical approaches are often required in view of low patient compliance. As per the present EASL guideline, pharmacotherapy is reserved for patients with NASH with significant fibrosis (stage F2 and higher). It is also recommended in patients with less severe disease, but at high risk of disease progression (i.e. with diabetes, Metabolic syndrome, persistently increased ALT, high necroinflammation on histology).

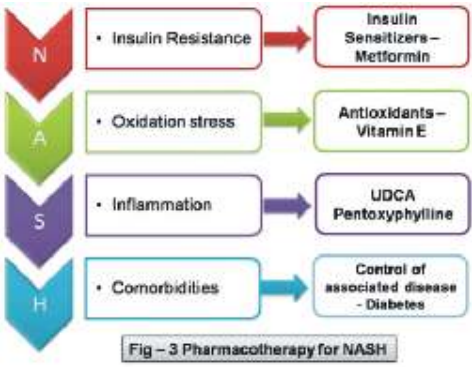

Fig – 3 Pharmacotherapy for NASH

Insulin sensitizer

For the treatment of NASH, use of thiazolidinediones (pioglitazone) has been most extensively evaluated. Thiazolidinediones are peroxisome proliferator - activatedreceptor (PPAR) cagonists with insulin-sensitizing effects. PIVENS trial compared low dose pioglitazone vs. Placebo[14] for 2 years in patients without overt diabetes. This study has showed that pioglitazoneimproved all histological features (except for fibrosis) and achieved resolution of NASH more often than placebo. Side effects seen with glitazones are weight gain, bone fractures in women and rarely congestive heart failure. Pioglitazone 30 mg/d may be considered in patients with biopsy-proven NASH with type 2 diabetes who do not have congestive heart failure or increased risk of fracture, although long-term effects have not yet been established.

Several smaller studies have reported reductions in plasma aminotransferase levels with metformin; however, improvement of liver steatosis, inflammation, and fibrosis has been reported in only a few small studies, with more recent studies finding no significant benefit. Metformin still holds clinical value in NASH because it controls hyperglycemia (common in these patients) and may reduce cardiovascular complications in patients with type 2 diabetes mellitus.

Antioxidants, cytoprotective and lipid lowering agents

Antioxidants reduce the generation of reactive oxygen species in the liver and reduce oxidative stress,are potential molecules in management of NASH. In clinical trials, vitamin E was well tolerated, and showed modest improvements in serum aminotransferase levels, improved steatosis and inflammation15.The tri-society practice guidelines recommend vitamin E 800 IU/day as a first-line therapy in nondiabetic adults with biopsy-proved NASH but caution against use of vitamin E in diabetic patients or patients with NAFLD without a liver biopsy.

Table 4 : **Pharmacologic therapies in the treatment of Non Alcoholic Steatohepatitis (NASH)[16]**

Treatment	Mechanism	Biochemical Effects	Histologic Effects	Comments
Orlistat	Enteric lipase inhibitor	↓ transaminase and insulin resistance	↓ Steatosis, inflammation	Improvement in inflammation, need to assess sustained weight loss & long term tolerability
Rimonabant	Weight loss, possible peripheral Effects	↓ Insulin resistance, triglyceride Levels, LFTs ↑ HDL and Adiponectin levels	↓ steatosis	Animal data, psychiatric side effects
Incretin analogues (Exendin-4)	Weight loss	↓ transaminase, insulin resistance, Hemoglobin A1C levels	↓ steatosis	Animal and pilot studies in NAFLD, extensively studied in type 2 diabetes mellitus
Thiazolidinediones.	PPAR-γ agonists	↓ transaminase, insulin resistance, And TNF-α levels ↑ Adiponectin levels	↓ Steatosis, inflammation and fibrosis	Side effects : weight gain, peripheral edema, cardiac, fractures, need for Maintenance therapy

Metformin	↑ Insulin resistance	↓ transaminase and insulin resistance	Limited improvement in inflammation, and fibrosis	Possible role in diabetic NASH
Vitamin E	↑ SAMe levels ↓ oxidative stress	↓ transaminase	Uncertain	Recommended by Tri-society guidelines
Betaine	↓ oxidative stress	↓ transaminase	↓ Steatosis, Inflammation and fibrosis	Pilot study only
UDCA	Hepatoprotective	No change	No change	Not beneficial in large RCT
Pentoxifylline	TNF α inhibitor	↓ transaminase, TNF - α levels	↓ Steatosis, inflammation	Pilot study only
HMG CoA - reductase Inhibitors	Improve lipid panel	↓ transaminase	Improved	Pilot study only
Ezetimibe	Blocks cholesterol absorption in intestine	-	↓ Steatosis and fibrosis	Animal data

UDCA although commonly used cytoprotective molecule for raised transaminases, has failed to show any significant histological improvements in patients with biopsy - proven NASH[17]. Pentoxyphylline, ananti - TNF - α agent with anti-inflammatory properties has shown benefit in various studies. However, larger RCTs are needed to validate the effects on NASH management. Statins may be confidently used to reduce LDLcholesterol and prevent cardiovascular risk, with neutral effect on liver disease. Similarly *n*-3 polyunsaturated fatty acids reduce both plasma and liver lipids, but there are no definite data to support their use specifically for NASH.

By improving obesity and diabetes, bariatric (metabolic) surgery reduces liver fat and is likely to reduce NASH progression; prospective data have shown an improvement in all histological lesions of NASH, including fibrosis[18] and has potential role in NASH management.

The optimal duration of therapy is unknown; in patients with increased ALT at baseline, treatment should be stopped if there is no reduction in aminotransferases after 6 months of therapy; in patients with normal ALT at baseline but with fibrosis, no definite guideline can be made at present and requires clinician's judgment. Optimizing diabetes mellitus control with insulin sensitizers such as metformin or glitazones, controlling hypertension with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and treating dyslipidaemia with statins and ezetimibe have been shown to benefit NAFLD patients. Cessation of smoking is advocated, as it is associated with more severe NASH.

When should I refer to a Specialist?

Most of the patients with NAFLD can be well managed by primary care physician by encouraging lifestyle modification and optimizing metabolic risk factors. However in selected group of patients with evidence of chronic liver disease, persistent elevated transaminase, family history of hepatocellular carcinoma, it is advisable to seek specialist opinion. As these high-risk patients may require further investigation, either by noninvasive or liver biopsy, to stage their disease and exclude other chronic liver diseases. Such patients may be candidates for pharmacotherapy if NASH is confirmed.

Emerging therapies in NASH

Most of the molecules, which are presently used in managing NASH, have little or no effect in improving fibrosis. Novel agents are emerging with targeted approach as anti-inflammatory, antifibrotic or insulin sensitizing properties (dual PPARa/d agonists, dual chemokine receptor [CCR] 2/CCR5 antagonists and fatty acid/bileacid conjugates) and antifibrotic agents (anti-LOXL2 monoclonal antibodies). These are being tested in late-phase RCTs in NASH and appear promising [listed below in chart]. A synthetic farnesoid X receptor agonist, obeticholic

Acidhas shown improvement in liverhistology of NASH, including liver fibrosis, which was not seen with other treatments, including vitamin E or pioglitazone. Many other classes of drugs are indevelopment and some promising phase 2 results have been seen. Long-term studies are essential to establish safety and the efficacy of such novel agents.

CCR; Chemokine receptor

Table 5 : **New drugs for NASH by primary mechanism of action[19]**

Drug Class	Primary Proposed Mechanism of Action	Examples
FXR agonist	Carbohydrate, lipid metabolism, and regulation of insulin sensitivity	Obeticolic acid (Phase III)
Insulin sensitizers	PPAR alpha/delta agonists GLP-1 receptor agonists	Elafibranor (GFT505) Saroglitazar (Phase II) Liraglutide (GLP-1 analogue)
Lipid lowering agents	N-3 PUFAs Fatty acidbile acid conjugates LXR-a inhibitor	Ethyl-eicosapentanoic acid Aramchol (Phase IIb) Oltipraz
Antioxidants	GSH repletion	Cysteamine
Antiinflammatory	Caspase inhibitor CCR 2 and 5 antagonists	Emricasan and GS-9450 Cenicriviroc (Phase II)
Antifibrotic agents	Monoclonal antibody against LOXL2 Galectin-3 inhibitor NOX1-NOX2 inhibitor	Simtuzumab (Phase II) GR-MD-02 GKT137831

Abbreviations : EPA-E, ethyl-eicosapentaenoic acid; FXR, farnesoid X receptor; GLP-1; glucagonlike peptide-1; GR-MD-02, galactoarabino - rhamnogalacturnate; GSH, glutathione; LOXL2, lysyl oxidaselike-2; LXR-a, liver X receptor alpha; n-3 PUFAs, n-3 polyunsaturated fatty acids; SGLT2, sodium glucose-dependent renal transporter

To Summarize -

1. NAFLD is a hepatic manifestation of a metabolic syndrome.
2. Ultrasonography is a preferred first line screening procedure for NAFLD.
3. Transient elastography is a better non-invasive assessment for advanced fibrosis.
4. Lifestyle modification including healthy diet and exercise for weightloss aremainstay of NAFLD treatment.
5. Present medications reduce steatosis / necroinflammation but will not change fibrosis.
6. NAFLD patients with advanced liver fibrosis or cirrhosis should be referred to specialist care.
7. Newer molecules in pipeline are promising for long term management of NASH.

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