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Review Article

"NASH-Worldwide the Commonest Aetiology of Liver Cirrhosis"- a Review Article

SNE Jannat[1], MMSU Islam[2], MM Haque[3], I Imam[4], DS Ahmed[5]

Abstract:

NAFLD is defined by the presence of fat in the liver (>5% hepatocytes show macrovesicular steatosis) without evidence of other causes of fat accumulation in the liver such as alcohol use (< 20 g/d for women and <30 g/d for men), hepatitis C or certain medications. The spectrum of disease includes NAFL, NASH, cirrhosis and HCC. Disease progression depends on stages of fibrosis. Patients are usually referred with incidentally noted hepatic steatosis on imaging or elevated liver enzymes. Although liver biopsy is the gold standard for diagnosis but worldwide it's much under practiced and several non invasive tests are currently recommended to identify at risk NASH (≥ stage 2 fibrosis) or advance fibrosis who are at highest risk of developing to cirrhosis. Screening in high-risk populations - T2DM, obesity with metabolic complications, a family history of cirrhosis or significant alcohol use allows for interventions that may prevent future hepatic complications. Currently, about 38% of the global population has a diagnosis of NAFLD. The incidence of hepatic decompensation, HCC and death related to NASH cirrhosis are expected to increase 2-to 3-fold by 2030. NASH- cirrhosis is already the leading indication of liver transplantation worldwide. Currently no specific treatments is licensed for NASH, lifestyle modification and exercise, primarily weight loss is the key to management. The rising clinical and economic burden of NAFLD has highlighted the need for a streamlined approach to prevention, diagnosis, and treatment of the disease that has been discussed in this narrative review.

Key words: NAFLD, NASH, Fibrosis

Introduction:

Non-alcoholic fatty liver disease (NAFLD) is the hepatic manifestation of the metabolic syndrome[1(1)]. It is commonly associated with obesity, insulin resistance, dyslipidemia, central obesity and hypertension[2]. The global prevalence of NAFLD has grown immensely over the last few decades, in parallel with the epidemics of obesity and Type 2 Diabetes Mellitus (T2DM) affecting around one-third of the global population that imposes a significant socioeconomic burden[3,4].

Most patients remain asymptomatic with slowly progressive disease, but a minority progress to cirrhosis, liver failure and hepatocellular carcinoma (HCC)[5]. Because of the close association between NAFLD and metabolic syndrome; cardiovascular disease and extrahepatic malignancies remain the leading causes of death[6,7] in contrast to hepatic complications who developed cirrhosis8. The purpose of this review is to summarize the latest knowledge based on updated guideline, guidance recommendations and recent publications for the management of adult NAFLD.

Definitions:

NAFLD is a generic name that encompasses the spectrum of steatosis or non alcoholic fatty liver (NAFL) to non-alcoholic steatohepatitis (NASH), cirrhosis and HCC[9].

1. Dr. Syeda Nur-E-Jannat, MBBS, FCPS (Medicine), MD (Gastroenterology), Assistant Professor, Department of Gastroenterology, Dhaka Medical College, Dhaka.

2. Dr. M. M. Shahin-Ul-Islam, MBBS, FCPS (Medicine), MD (Gastroenterology), Associate Professor (CC), Department of Gastroenterology, Faridpur Medical College, Faridpur.

3. Dr. Mohammad Majharul Haque, MBBS, FCPS (Medicine), MD (Gastroenterology), Assistant Professor, Department of Gastroenterology, Dhaka Medical College, Dhaka.

4. Dr. Iftekhar Imam, MBBS, MD (Gastroenterology), Specialist, Department of Gastroenterology & Hepatology, United Hospital Limited, Dhaka.

5. Dr. Dewan Saifuddin Ahmed, MBBS, FCPS (Medicine), MD (Gastroenterology), Professor, Department of Gastroenterology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh.

Address of the correspondence:

Dr. Syeda Nur-E-Jannat, MBBS, FCPS (Medicine), MD (Gastroenterology), Assistant Professor, Department of Gastroenterology, Dhaka Medical College, Dhaka. Phone: +8801819442631, Email: jannatdmc@yahoo.com

NAFLD: Hepatic steatosis (>5% hepatocytes show macrovesicular steatosis) in the absence of other causes of liver disease and alcohol use <30 g/d in males and <20 g/d in females[9].

NASH: Defined on liver histology with NAFLD activity score (NAS) ≥5[10]. NAS is calculated by sum of the scores for steatosis, lobular inflammation and ballooning, used to evaluate histological changes over time rather than to serve as diagnostic criteria for NASH[10]. Steatosis grade is defined by percentage of hepatocytes showing fat on liver histology. Grade 1 (5-33%), grade 2 (34-66%) and grade 3 (≥66%)[10], usually macrovesicular; however, in 10% of patients with NAFLD microvesicular steatosis may also be present[11]. Lobular inflammation is graded by number of inflammatory foci per 200 X field, as grade 1 (<2 foci), grade 2 (2-4 foci) and grade 3 (>4 foci)10. Hepatocyte ballooning is graded by number of ballooned hepatocytes, as grade 1 (few balloon cells), and grade 2 (many ballooned cells)[10].

Hepatic Fibrosis: Fibrosis stage is defined as stage 1 with peri-sinusoidal or portal fibrosis, stage 2 with peri-portal fibrosis, stage 3 as bridging fibrosis and stage 4 with cirrhosis[10].

Recently, it has been suggested that the term NAFLD does not reflect the heterogeneous pathogenesis or various courses of fatty liver disease. In 2019, a consensus by 32 experts suggested an alternative terminology, metabolic (dysfunction)-associated fatty liver disease (MAFLD), to more accurately reflect the pathogenesis of this disease[12].

Variants of NAFLD:

Lean NAFLD: NAFLD in people with normal body weight (BMI <23kg/m^2 for Asians or <25 kg/m^2 for Westerners)[9]. More prevalent in Asia[13]. Compared to healthy people, had higher metabolic syndrome occurrence, diastolic BP, HbA1c, and insulin resistance[14]. Independant stronger risk factor for higher rates of all-cause mortality, cirrhosis, and HCC than obese NAFLD[14].

Metabolically healthy NAFLD: Does not meet any metabolic syndrome criteria[15].

Metabolic (dysfunction) Associated Fatty Liver Disease (MAFLD): In addition to steatosis they have one of the following three criteria: overweight/obesity, type 2 Diabetes Mellitus (DM) and evidence of metabolic dysregulation.

Natural history of NAFLD:

Disease progression: The transition from NAFL to NASH is quite dynamic. Fibrosis progression is significantly slower in NAFL than NASH, requiring 14 years per stage of fibrosis, whereas in NASH, each stage progresses over 7 years[16]. Approximately 20% of NASH may be classified as "rapid progressors," in whom each stage progresses in less than 7 years. Predictors of rapid progression may include higher serum ALT, presence of diabetes, family history of cirrhosis in first-degree relatives and possibly genetic susceptibility.

Only 20% of individuals with NAFLD have NASH, and 20% of NASH may progress to cirrhosis over 3–4 decades[16] with a risk of development of HCC~1.5%–2% per year (Figure-1)[17]. Therefore, HCC screening and surveillance are routinely recommended with ultrasound with or without alpha-fetoprotein (AFP) every 6 monthly in NASH-related cirrhosis[17].

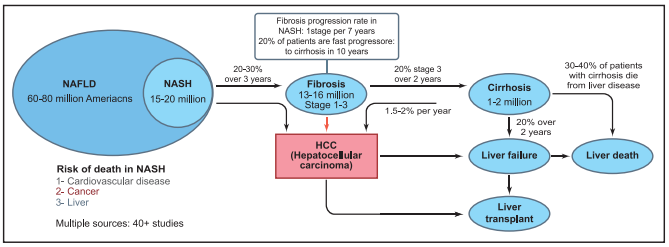

Figure-1: Natural history of NAFLD

Extrahepatic complications of NAFLD

Cardiovascular disease is the leading cause of mortality followed by extrahepatic cancer, then liver related death[18]. In a Japanese cohort, the adjusted hazard ratio for CVD was~10-fold higher in non-obese individuals with NAFLD compared with those without NAFLD[19]. Cancer in stomach, pancreas and colon increases by 2-fold and trend toward a younger age at diagnosis[20].

Epidemiology:

Globally NAFLD is currently the most common chronic liver disease. It's prevalence has increased by more than 50% over the last three decades, from 25.3% in 1990-2006 to 38.0% in 2016-2019[4].

Regional trends:

The pooled prevalence of NAFLD in 1990-2019 was 33.8% in South Asia, 33.1% in Southeast Asia, 29.7% in East Asia, and 28.0% in Oceania[4]. The prevalence of NASH in Europe was 4.0%[21], the highest NAFLD prevalence rate was observed in Latin America (44.4%)[4].

NAFLD in special population:

Among patients with T2DM, the prevalence of NAFLD and NASH is around 56% and 37% respectively with around twice higher risk of developing cirrhosis and HCC compared to non-diabetic populations[22,23]. In polycystic ovarian syndrome, HIV infected patients the prevalence of NAFLD is also considerable at around 43%[24] and 22-42%[25] respectively. Patients with NAFLD who continue alcohol consumption have higher stages of fibrosis at presentation, and worse prognosis[26,27].

NAFLD is the main driver of an increase in chronic liver disease among adolescents and young adults[28]. Children of obese mothers seem to be at a higher risk of developing NAFLD potentially of a more advanced severity[29].

Cirrhosis and its complications:

NASH is emerging as one of the leading causes of cirrhosis, cirrhotic complications, HCC and liver-related death[30]. It's true burden has traditionally been underestimated, as NAFLD-related cirrhosis is often labelled as "cryptogenic cirrhosis" and "other cirrhosis", which are often burned-out NASH in reality[31]. Modelling studies have estimated that both compensated and decompensated NAFLD related cirrhosis will be increased by 2-3 fold in most countries between 2016 and 2030, with an increase ranging from +64% in Japan to +156% in France[2,32,33].

NAFLD has increasingly been identified as the cause of HCC, accounting for 0-3% of cases in the 1990s to 12-29% in the 2010s in other European studies[34], and in Italy, already the top aetiology of HCC in 2023[35]. The aetiologies of HCC in Asia are also undergoing a change from viral to non-viral causes–predominantly NAFLD[36]. In a recent report from six countries in South America, NAFLD is now the most common aetiology in HCC cases[37].

NASH-related cirrhosis is already the leading indication for liver transplantation (LT) in women and those >65 years of age in the United States[38,39] and a rapidly increasing indication elsewhere in the world[40]. In the European LT Registry, NAFLD-related cirrhosis represented up to 8.4% of LT for cirrhosis in 2016[41].

Molecular and cellular pathogenesis:

When energy intake exceeds metabolic needs and disposal capacity, carbohydrates, in the form of dietary sugars (eg, fructose, sucrose, and glucose) and saturated fat drive the formation and accumulation of intrahepatic triglyceride by de novo lipogenesis (DNL) 42-43 (Figure-2)

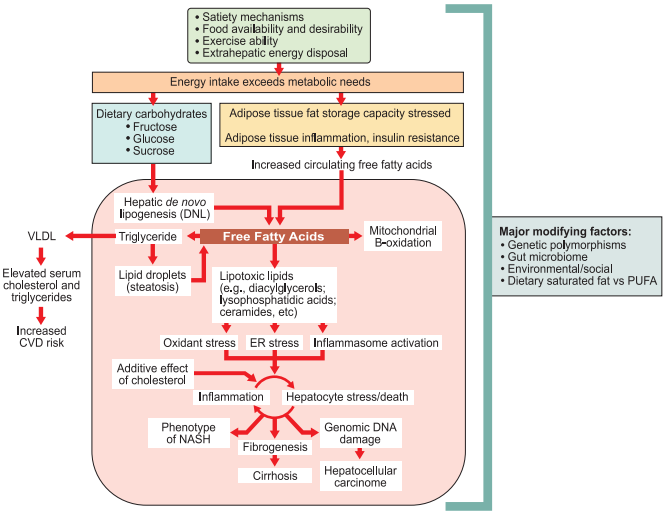

Figure-2: Metabolic mechanism of NAFLD

Insulin resistance is universal and is present in the liver, adipose tissue, and muscle[44]. Skeletal muscle insulin resistance, one of the earliest defects associated with metabolic syndrome and prediabetes[45], occurs due to ectopic lipid deposition in skeletal muscle, leads to decreased insulin-stimulated glucose transport and muscle glycogen synthesis in skeletal muscle and divert glucose to liver for DNL[46,47]. Development of hepatic insulin resistance, where insulin activation of glycogen synthase is impaired, also redirect glucose into lipogenic pathways[48]. Adipocyte dysfunction due to an oversupply of fat to adipocytes, activates inflammatory pathways and causes insulin resistance leading to increase in fatty acid delivery to the liver promoting hepatic steatosis and dyslipidemia[48].

Genetic polymorphisms is associated with the development of NAFLD, NASH-cirrhosis, and HCC by impacting hepatocyte lipid metabolism who have metabolic risk factors such as obesity, diabetes, metabolic syndrome as well as other environmental factors, like alcohol and smoking[49]. The PNPLA3 gene is a major driver, I148M polymorphism of PNPLA3 impairs lipolysis of triglyceride in lipid droplets[50]. Other genetic factors are also involved in NASH progression(Figure-3).

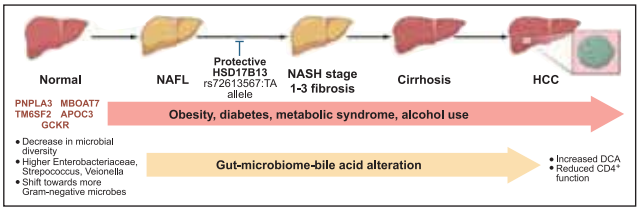

Figure-3: A gene-environment nexus drives the risk of cirrhosis and HCC in NASH

Gut microbiome dysbiosis is emerging as a crucial factor in the development of NAFLD and NAFLD-HCC by dysregulating the gut–liver axis(Figure-4)[51], leading to increased intestinal permeability and unrestrained transfer of microbial metabolites into the liver where bacteria can stimulate hepatic immune cells, activate inflammation pathways, and eventually proceed to NAFLD/NAFLD-HCC[52,53]. Recently, a universal gut microbiome signature in NASH-cirrhosis has also been described[53]. Two types of bacteria, *Prevotella copri and Bacteroides vulgatus*, have been shown to drive the production of branched chain amino acids (BCAA) in the gut which is raised in people with insulin resistance[54].

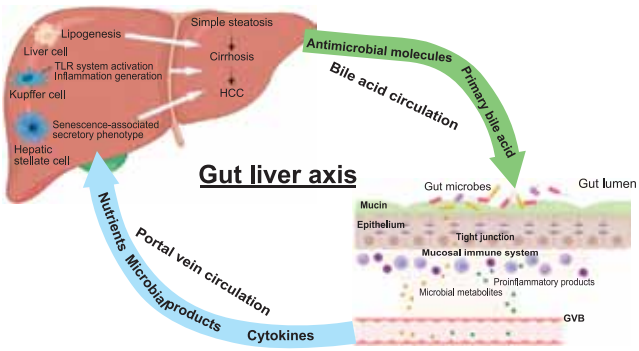

Figure-4: Gut-Liver axis

Co-morbid conditions associated with NAFLD:

Obesity: Pattern of body fat distribution is an important determinant than BMI alone. Android body fat distribution (increased truncal subcutaneous fat and visceral fat) confers a higher risk of insulin resistance, CVD and hepatic fibrosis, irrespective of BMI[55,56]. In contrast, gynoid body fat distribution (increased subcutaneous body fat) predominantly in the buttocks, appears to be protective against NAFLD[57]. Visceral fat is more metabolically active and inflammatory than subcutaneous fat, mediates the majority of this risk[58].

Type 2 diabetes mellitus (T2DM): T2DM is the most impactful risk factor for the development of NAFLD, fibrosis progression and HCC[59,60]. Insulin resistance is the key pathophysiology for both T2DM and the progression of histological lesions in NAFLD; NAFLD is present in almost 30-70% of patients with T2DM[61], whereas 25% of patients with NAFLD have T2DM[60]. Even in absence of overt diabetes, NAFLD is associated with reduction of insulin sensitivity in early course of disease[44] and 2-5 fold increase risk of DM[62]. Diabetic patients have almost 3- to 5-fold higher risk to be hospitalized or die because of NASH-cirrhosis[63]. So all patient with NAFLD and T2DM should be screened for T2DM and advanced fibrosis respectively. Both drive an increase risk in CVD (2 fold), CKD (3.5 times) and malignancy[64].

Hypertension: Hypertension is commonly associated. Its incidence ranges from 6.5/100 person-years (NAFLD) to 14.5/100 person-years (NASH cirrhosis)[8].

Dyslipidemia: NAFLD is associated with twice increased risk of dyslipidemia characterized by decreased serum HDL and increased serum TG levels leading to CVD[9]. Study showed that incidence of CVD was similar in both NASH and NAFLD, mean LDL did not differ but small dense low-density lipoprotein (sdLDL) cholesterol was more atherogenic and was significantly higher (sdLDL-C > 25 mg/dL) among patients who had CVD compared with those who didn't[65].

Obstructive sleep apnoea (OSA): OSA is associated with NAFLD and NASH cirrhosis[66,67]. Intermittent hypoxia, a critical consequence of OSA, has been linked to mitochondrial dysfunction[66], dysregulation of glucose and lipid metabolism[68], worse insulin resistance[69], and increased hepatic DNL[70].

Cardiovascular disease (CVD): NAFLD is independently associated with increased risk of acute coronary syndrome and stroke and cardiac death- the leading cause of mortality in patient with NAFLD[65]. A strong association exists between NAFLD and atherosclerotic heart disease, heart failure, and arrhythmias, particularly atrial fibrillation[71,72]. Aggressive management of CVD risk factors like hypertension, dyslipidemia, hyperglycemia and promoting smoking cessation with the goal of reducing CVD morbidity and mortality is critical to improving outcomes in patients with NAFLD[18,20].

Chronic kidney disease (CKD): Prevalence and incidence of CKD is higher among patients with NASH and advanced fibrosis[9], mostly associated with microvascular diabetic complications[73].

Initial evaluation of NAFLD:

Patients with NAFLD are most commonly referred with incidentally noted hepatic steatosis on imaging or elevated liver chemistries. Aminotransferases may be normal in >50% patients with NASH and elevated in NAFLD patients without NASH[74,75].

History & clinical examination regarding weight gain, other co-morbidities like HTN, DM, Dyslipidemia, CVD, CKD, hypothyroid, OSA, PCOS, hypogonadism, GH deficiency, recent or current medications, detailed

alcohol history & family history - T2DM, NAFLD, cirrhosis should be noted. Detailed laboratory investigations includes CBC with platelets, hepatic & renal panel, OGTT, fasting lipid profile, TSH, HCV, HBV & other investigations to exclude other causes of elevated aminotransferase like Wilson disease, AIH, haemochromatosis should be done.

Assessing the severity of liver disease:

Who should be screened ?

Screening in high-risk populations - T2DM[22,76], obesity with metabolic complications[77], a family history of cirrhosis[78], or significant alcohol use[79], allows for interventions that may prevent future hepatic complications[23].

Liver biopsy: Liver biopsy remains the reference standard for the grading and staging of NASH[80], is invasive and carries a risk of complications[81], is limited by sampling variability[82] and high observer dependent variability in pathological reporting[83]. However real-world rates of biopsy in NASH patients have been found to be low (<2%)[84]. Current evidence does not support routine liver biopsy for diagnosis of NAFL/NASH, but may be considered in whom competing etiologies for NASH and the presence and/or severity of coexisting CLDs cannot be excluded without a liver biopsy[85].

Biomarkers / Non Invasive Tests (NITs): NIT is useful to rule out people unlikely to have advanced liver disease, without need for biopsy[86]. According to clinical context of use, non-invasive imaging, blood tests are becoming more important for staging and quantifying disease.

Identification of NAFLD:

Ultrasonogram although most widely used, has low sensitivity in detecting less severe steatosis[87]. CT scan lacks specificity and sensitivity, and exposes the patient to ionizing radiation. The controlled attenuation parameter (CAP) provides a useful indication of NAFLD, but the gold standard has become MRI-derived proton density fat fraction (MRI-PDFF), for its ability to quantify fat content[88].

Assessment of degree of fibrosis:

Fibrosis is assessed by measuring indirect biomarkers, primarily based on liver stiffness measurement (LSM)[89]. It is assessed by elastography, with vibration controlled transient elastography (VCTE) (FibroScan) imaging machine the most commonly used[90]. Patients with higher liver stiffness also have higher liver-related mortality, suggesting that this is a prognostic biomarker[91]. Magnetic Resonance Elastography (MRE) is more sensitive than VCTE in the detection of fibrosis stage ≥2[92].

Few blood-based biomarkers have be developed to asses stages and progression of fibrosis[93] Table I. Although FIB-4 is statistically inferior to imaging based elastography methods, still it is recommended as the first line assessment tool for general practitioners due to its simplicity and minimal costs.

Table-I: Indirect fibrosis biomarkers panels[93]

Tests	Description
AST: ALT ratio	AST (IU/L) / ALT (IU/L)
AST to platelet index	AST (IU/L)/(ULN)/platelet count ratio (x109 /L) x 100
BARD score	Weighted sum of BMI≥28 = 1 point, AST/ ALT ratio ≥0.8 = 2 points, T2DM=1
FIB-4 score	Age x AST (IU/L)/platelet count (x109 /L) x √ ALT (IU/L)
NAFLD fibrosis (NFS)	−1.675+0.037 x age (years)+0.094 x score BMI (kg/m2)+1.13 x IFG or T2DM (yes=1, no=0)+0.99 x AST/ALT ratio − 0.013 x platelet (x109 /L) − 0.66 x albumin (g/dL)

Combination of various blood based biomarkers along with imaging can be used for more accurate assessment of degree of steatosis, inflammation and fibrosis particularly to identify following clinically relevant NAFLD categories.

Identify 'At risk NASH':

where steatohepatitis is active and there is moderate fibrosis (NAS≥4, Fibrosis stage ≥2)- they are likely to progress to cirrhosis—is particularly important for identifying candidates for treatment[94].

The FAST score, which combines liver stiffness and CAP from the FibroScan and the circulating biomarker (AST:ALT ratio), above 0.67 indicates moderate fibrosis requiring intervention while below 0.35 would exclude fibrosis[95]. MEFIB index (FIB-4 ≥1.6 plus MRE ≥3.3 kPa), yields a 97.1 positive predictive value for identifying stage 2 fibrosis[96] and has been shown to be superior to FAST[97].

Identification of advanced fibrosis:

FIB-4 index and VCTE are widely used for identifying advanced fibrosis-**bridging fibrosis (stage 3)** or

cirrhosis (stage 4)- who are likely to see outcomes worsen significantly[98].

Recent meta-analysis suggested that combining FIB-4 and LSM-VCTE sequentially, **FIB-4 <1.3; LSM-VCTE <8.0 kPa,** can be used to rule out advanced fibrosis and FIB-4 ≥3.48; LSM-VCTE ≥20.0 kPa can diagnose cirrhosis without need of liver biopsy with 95% specificity[99]. LSMs by VCTE **between 8 and 12 kPa** indicates fibrotic NASH and LSM >12 kPa is associated with a high likelihood of advanced fibrosis[98,99].

MRE ≥5 kPa has 95% specificity for diagnosis of cirrhosis and associated with increased risk of hepatic decompensation (U,V) Enhanced liver fibrosis (ELF) test (combining procollagen III N-terminal peptide, hyaluronic acid, tissue inhibitor of metalloproteinase 1) with score of ≥9.8 reliably identifies advanced fibrosis and ELF ≥11.3 associated with increased risk of hepatic decompensation with cirrhosis[100].

A positive **MEFIB** (FIB-4 ≥1.6 plus MRE ≥3.3 kPa) has been linked to increased risk of hepatic decompensation, and a negative MREFIB has a 99% negative predictive value for a 5-year risk of hepatic decompensation[101].

Who should be referred to gastroenterologist/ hepatologist ?

In the primary care setting, if FIB-4 <1.3, patients with ≥2 metabolic risk factors, particularly with pre-DM, T2DM can be followed and reassessed periodically with FIB-4 every 1–2 yearly (Figure-5) If FIB4 ≥1.3, a secondary assessment should be done preferentially VCTE or ELF initially and those with persistently elevated aminotransferases (>6 mo) should be referred to gastroenterologist/hepatologist[102].

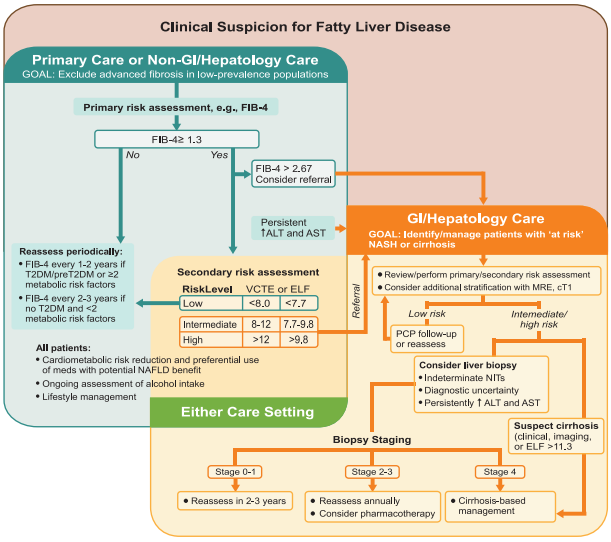

Figure-5: Algorithm for the evaluation of patients at risk for or with established NAFLD across practice settings.

Treatment:

Weight loss: Weight loss is the key to improve hepatic steatosis, achieved by a combination of a daily calorie reduction by 500–1000 kcal and moderate-intensity exercise[85]. Weight loss of at least 3%–5% of body weight improves steatosis and 7%–10% improves the majority of the histopathological features of NASH, including fibrosis[85,103].

Diets with limited carbohydrates and saturated fat and enriched with high fiber and unsaturated fats (e.g., Mediterranean diet, intermittent fasting) offers additional cardiovascular benefits[104]. The best evidence of benefit comes from the Mediterranean diet containing plentiful intake of olive oil, vegetables, fruits and nuts, legumes, whole grains, fish and seafood, and a low intake of red meat and especially processed meat, along with reduced carbohydrates intake (40% of the calories vs 50%–60% in a typical low-fat diet), especially sugars.

Exercise, independent of weight loss, has hepatic and cardiometabolic benefit[105,106]. Regular moderate exercise at least 5 times per week for a total of 150 minutes per week or an increase in activity level by more than 60 minutes per week can prevent or improve NAFLD[106,107]. In patient with NASH cirrhosis and obesity weight loss and regular physical exercise reduce portal pressure[108], improve frailty, sarcopenia and quality of life[109].

Cardiovascular risk reduction: Commonly associated metabolic disease like diabetes, hypertension, dyslipidemia, coronary artery disease should be addressed aggressively as they are at high risk for cardiovascular morbidity and mortality.

Statins are safe and recommended for CVD risk reduction in patients with NAFLD across the disease spectrum, including compensated cirrhosis[110] and may be considered in decompensated cirrhosis with high CVD risk with careful monitoring[111]. Statins also provide anti-inflammatory, anti-oxidant, and anti-thrombotic benefits by targeting pathways that are activated in the pathophysiology of NAFLD[112].

In patients with NAFLD and hypertriglyceridemia (eg, > 500 mg/dL), fibrates, or a combination of fibrates with omega-3 fatty acids or icosapent ethyl, reduce the risk of pancreatitis. Fibrates may also improve atherosclerotic CVD outcomes when triglyceride ≥ 200 mg/dL and HDL-C <40 mg/dl. In high-risk individuals, icosapent ethyl is indicated as an adjunct to statin therapy to

reduce atherosclerotic CVD risk. Pioglitazone used for glycemic control has concomitant beneficiary effect on lipid profile[102].

Bariatric surgery: Currently accepted criteria for bariatric surgery are BMI ≥40 kg/m^2 irrespective of metabolic comorbidities or BMI ≥ 35 kg/m^2 with comorbidities (T2DM or prediabetes, uncontrolled hypertension, osteoarthritis of hip or knee, urinary incontinence), NAFLD/NASH is increasingly accepted as a co-morbid condition benefiting from bariatric surgery[113]. Bariatric surgery should be considered as a therapeutic option in patients who meet criteria for surgery, as it effectively resolves NAFLD or NASH in the majority of patients without cirrhosis, induce sustained weight loss of up to 30%, cure diabetes, and decrease all-cause morbidity and mortality[114,115]. Study shows resolution of NASH without worsening of fibrosis occurred in 80% of patients 1 year following bariatric surgery,which was maintained at 5 years[116].

Pharmacological treatments:

Despite the rising prevalence and serious potential clinical consequences, there are currently no treatments licensed for NASH. Treatment relies on lifestyle changes, primarily weight loss. There are medications approved for other indications that have shown benefits for NASH in clinical trials and should be considered for patients with biopsy-proven NASH and fibrosis under specific circumstances.

Vitamin E: At a dose 800IU/day improves steatosis, but no proven benefit on fibrosis. It can increase the risk of Hemorrhagic stroke & prostate cancer[117,118].

Pioglitazone: At a dose of 30–45 mg/ day improves steatosis activity and NASH resolution, may improve fibrosis, improves insulin sensitivity, can prevent T2DM, stroke & reduces CV risk. It may cause weight gain, exacerbate heart failure & osteoporosis[119, 120].

Liraglutide: At a dose of 0.6–3 mg/day subcutaneously has no proven impact on fibrosis but improves steatosis & insulin sensitivity, causes weight loss, reduces CV risk & may slow progression of renal disease, it may causes gall stone related pancreatitis[121].

Semaglutide: At a dose of 0.4 mg subcutaneously daily or 0.25–2.4 mg subcutaneously weekly has no proven benefit on fibrosis, but may slow down its progression, improves steatosis activity, causes resolution of NASH, improve insulin sensitivity, causes weight loss, improves CV and renal outcomes, stroke prevention, it may causes gall stone related pancreatitis[122].

Tirzepatide: It reduces steatosis, improve insulin sensitivity, causes significant weight loss, it may causes gall stone related pancreatitis[123, 124].

Sodium glucose cotransporter-2 inhibitor(SGLT-2i): Reduce steatosis, may improve insulin sensitivity, improves CV and renal outcomes, has beneficial effect in heart failure, causes modest weight loss, it increases the risk of genitourinary yeast infection, volume depletion & bone loss[123, 124].

Metformin[125], ursodeoxycholic acid[126], dipeptidyl peptidase-4[127], n-3 polyunsturated fatty acids[128], ezetimibe[129], fenofibrate[130] and silymarin[131] are well studied in NASH and should not be used as a treatment for NASH as they do not offer a meaningful histological benefit.

The farnesoid X receptor (FXR) is a ligand-activated transcription factor, involved in the control of bile acid synthesis and is also central to a number of pathways in the liver, affecting inflammation, fibrosis, lipid metabolism and glucose metabolism[132]. Obeticholic acid is a selective FXR agonist currently tested in a phase III trial. The main adverse event was pruritus and increase in LDL cholesterol, responsive to statin therapy[133].

Peroxisome proliferator-activated receptors (PPARs)-Lanifibranor, is generally well tolerated with mild weight gain under phase III trial[134,135].

Thyroid hormone receptor beta (THR-β- is crucial for liver homoeostasis. Resmetirom a THR-β agonist, have been shown to improve lipid metabolism[134,136]) liver stiffness, as well as reduction in LDL-cholesterol and ApoB[137].

Screening for HCC:

High-risk individuals like T2DM, medically complicated obesity, family history of cirrhosis, or more than mild alcohol consumption, should be screened for advanced fibrosis. Patients with NASH cirrhosis should be screened for gastroesophageal varices and HCC. Current evidence does not support routine screening and surveillance for HCC in patients with noncirrhotic NASH[102].

Conclusions:

There are still challenges to develop accurate, specific, meaningful imaging technology and circulating biomarkers for diagnosis, staging, monitoring disease progression. No specific drug therapy for NASH is still

recommended. As lifestyle modification is still the cornerstone of management- need extensive awareness that can make a real difference in outcome of NASH.

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