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REVIEW ARTICLE

NON ALCOHOLIC FATTY LIVER DISEASE: A SILENT GLOBAL EPIDEMIC

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Abstract:

Nonalcoholic fatty liver disease (NAFLD) is a common liver disease worldwide affecting adult as well as children with an increasing prevalence. It is associated with insulin resistance and frequently occurs with features of the metabolic syndrome. NAFLD is a spectrum, with NAFL (Non-alcoholic fatty liver) being the initial mildest form, NASH and cirrhosis is being at the other end of the spectrum. Mostly NAFLD is asymptomatic but may present with elevated liver enzyme levels to cirrhosis with its complications and hepatocellular carcinoma. Standard ultrasound including elastography may be used to detect steatosis. Though, liver biopsy is the gold standard for diagnosis of NAFLD but it is not frequently performed. NAFLD patients with evidence of nonalcoholic steatohepatitis and advanced fibrosis are at increased risk of adverse outcomes, including overall mortality. Life style modification and weight loss remains the cornerstone of the management of NAFLD. There are no approved pharmacological drugs for the treatment of NAFLD till now. Although several promising drugs are on the horizon, more trials are needed to validate these medications.

Keywords: *Nonalcoholic fatty liver disease, NAFLD, NASH, steatosis, steatohepatitis, treatment.*

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Introduction:

Nonalcoholic fatty liver disease (NAFLD) is now the most common chronic liver disease in our clinical practice causing major public health problem globally.[1-4]Fatty liver disease occurs when excessive fat accumulates in the liver. Nonalcoholic fatty liver disease (NAFLD) refers to a condition where excess fat accumulates in more than 5% of liver cells in individuals who drink little or no alcohol (defined as <20 g/d for female or < 30 g/d for male) and absence of other secondary causes e.g.drugs, starvation & monogenic disorders.[2]

NAFLD is the term that includes a spectrum of progressive liver disorders that ranging from simple fatty liver (Steatosis) to nonalcoholic steatohepatitis (NASH) with presence of inflammations, fibrosis(with various degree of severity) leading to cirrhosis of liver & complications.[2,3]

Easy access to calorie rich food, lack of physical exercise together with current epidemics of overweight,obesity, insulin resistance and diabetes mellitus (DM) are responsible for NAFLD leading to a substantial health burden in Bangladesh as in the globe.[4,5] NAFLD is now becoming the leading cause of cirrhosis of liver, hepatocellular carcinoma (HCC) and liver transplant all over the world.[5]

NAFLD frequently coexists with metabolic syndrome and plays important role in causing hepatic and extrahepatic disorders like cardiovascular disease which is the leading cause of death in NAFLD.[1,3]

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Metabolic syndrome is defined if three or more of the following five criteria are present: waist circumference over 102 cm (40 inches)in male or 89 cm (35 inches) in female, blood pressure over 130/85 mmHg, fasting triglyceride (TG) level over 150 mg/dl, fasting high-density lipoprotein (HDL) cholesterol level less than 40 mg/dl (men) or 50 mg/dl (women) and fasting blood sugar over 100 mg/dl (National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III definition).[6,7]

We searched systematically in different published literatures at national and international level using various search engine like Google, PubMed and Bangladesh Journals Online (BanglaJOL) etc to collect recent knowledge on nonalcoholic fatty liver disease (NAFLD). The aim of this review is to present up to date information on prevalence, pathology, diagnosis and treatment of NAFLD.

Prevalence:

NAFLD affects peoples of all ages and sex including adolescent and children. The prevalence of NAFLD in general population is about 25-30% but it varies with race, ethnicity,geographical and rural-urban differences.[2,4]The prevalence of NAFLD was estimated between 17%-46% (on average about 25%) in western adults.[8]Prevalence in China, Japan,Korea and middle east is almost similar with western countries.[9] A recent meta-analysis of studies in India showed the prevalence of NAFLD is 38.6% in adults and 35.4% in children.[10] One study from India shows the prevalence of NAFLD is higher in urban populations (16-32%)than that of rural community (9%).[6] In Bangladesh an ultrasound based study observed that 18.5% of people had NAFLD. Among them it was detected in 36.93% of obese and 7.1% of non-obese persons.[11] Another study in Bangladesh showed the prevalence of NAFLD was 33.86% i.e. one-third of population and highest in between the age group of 31-60 years.[12,13]

Pathophysiology of NAFLD and NASH:

Pathogenesis of NAFLD and NASH is multifactorial complex process. It has been suggested that progression of NAFLD to NASH is a two-step process.First step is hepatic fat deposition which will initiate the resistance to insulin. Second step of process is various cellular and molecular changes which includes oxidative stress and fatty acid oxidation in liver. These reactions are due to hyperinsulinemia, cytokine induced injury, change in immune functions etc.[14]When there is imbalance between nutrient intake and metabolic needs and proper disposal, carbohydrates like dietary sugars lead to excess production and accumulation of fat in liver cells from de novo lipogenesis (DNL). The saturated fat consumption is a higher risk to develop the disease than that of unsaturated fat.[2] Simple fatty liver (NAFL) i.e. only fat deposition in hepatocytes with no or minimal cellular inflammation does not usually do any harm. Majority of NAFLD patients have simple fatty liver. If NAFL is not managed properly, inflammation of hepatocytes will progress to nonalcoholic steatohepatitis (NASH) and cellular damage. These cellular damage can lead to accumulation of fibrous tissue in the liver (fibrosis) which can ultimately lead to cirrhosis of liver.[8]Among cirrhotic patient clinical decompensation develops in 3-20% of per year.[2]

Common causes of fatty liver :[6,14,15]

Macrovascularsteatosis	Microvascularsteatosis
Excessive alcohol intake	Acute fatty liver of pregnancy
HCV infection (Genotype 3)	HELLP syndrome
Wilson' s disease	Reye's syndrome
Starvation	Inborn errors of metabolism
Total parenteral nutrition (TPN)	Medication:
Intestinal bypass surgery	Valproic acid
Medication:	Anti-retroviral drugs
Corticosteroids, Amiodarone, Methotrexate,Tamoxifen, Tetracycline, Vinyl chloride etc.	

Risk factors for NAFLD:[15]

Common conditions	Other conditions associated with NAFLD
Obesity	Hypothyroidism
Type 2 DM (T_2DM)	Hypopituitarism
Dyslipidemia	Hypogonadism
Metabolic syndrome (MetS)	Obstructive sleep apnea (OSA)
Polycystic ovarian syndrome (PCOS)	Pancreatoduodenal resection
	Psoriasis

Clinical features:

NAFLD patients do not have any symptoms in majority cases but some of them may have mild right upper abdominal discomfort, weakness, hepatomegaly, acanthosisnigricans, lipomatosis. Diagnosis of NAFLD or NASH is very often made by getting abnormal LFTs like raised ALT & AST and finding bright liver on ultrasound image incidentally. A good number of patients present with chronic liver disease like cirrhosis and its complications.[14]

Laboratory findings:

In NAFLD, ALT and AST level may either normal or elevated commonly. ALT elevation is more common than AST elevation in the range of 2 to 3 times of upper limits of normal. Level of ALT tends to be higher in NASH than simple NAFL. The AST/ALT ratio typically less than 1 and this helps to distinguish NAFLD from alcoholic liver disease (ALD).Serum Ferritin is elevated in NAFLD in most of cases but transferrin saturation is elevated in fewer cases (6-11%).[14,15]In NASH, in addition to ALT,AST level Alkaline phosphatase (ALP), $^{-}$-glutamyl-transpeptidase (GGT) may be elevated. NASH is more likely to have level of homeostasis model assessment of insulin resistance (HOMA-IR).(Normal Range of HOMA-IR is 0.5–1.4, above1.9 indicates early insulin resistance and above 2.9 indicates significant insulin resistance).[15] Antinuclear antibodies (ANA) are detected in 25-30% of NASH patients. There are no definite patterns of dyslipidemia, although high levels of triglyceride is usually found.[6]

Imaging in NAFLD:

Different imaging studies can be used to diagnose the fatty liver disease but none of them are routinely used to differentiate the subtypes of NAFLD or NASH.

Ultrasound (US):

Ultrasound (US) is the cheapest method and most commonly used in clinical practice. US shows hyperechoic liver parenchyma or bright liver, sensitivity and specificity of US are 89% & 93% respectively.[14]In the setting of morbid obesity sensitivity and specificity of US are reduced. It has low sensitivity for lesser degree of steatosis. Steatosis may have similar echogenicity as fibrosis.[2]

Grades of fatty liver on ultrasound:[4]

Grade	Findings
Grade- I	Increased echogenicity of liver parenchyma in relation to spleen and kidney
Grade- II	Grade I + blurring of intrahepatic vascular structures
Grade- III	Grade II + deep attenuation of ultrasound waves.Diaphragm cannot be easily distinguished from the hepatic surface

CT, MRI imaging:

There are costly imaging modalities to detect the steatosis but are less sensitive to detect inflammation or fibrotic changes in liver. Magnetic resonance spectroscopy (MRS) & MRI proton density fat fraction (MRI-PDFF) have higher sensitivity and considered gold standard to quantify hepatic fat, but not yet widely available.[2,6,14]

Transient elastography (Fibroscan):

Fibroscan of liver is now the most commonly used method to estimate hepatic stiffness and the degree of liver fibrosis.Advanced fibrosis can be ruled out if liver stiffness measurement (LSM) is less than 8 KPa. LSM between 8 and 12 KPa indicates fibrotic NASH and greater than 12 KPa indicate advanced liver fibrosis. The controlled attenuation parameter (CAP) value can be used to assess statosis.[2] A meta-analysis showed that the cut-off value for steatosis> S_0 was 248dB/m and grade S_1 was 268 dB/m.[14] MR elastography (MRE) is more sensitive than fibro scan, thereby considered as most accurate imaging to detect fibrosis in NAFLD.[4]

Other noninvasive investigations:

Noninvasive tools to predict advanced fibrosis are NAFLD fibrosis score (NFS), Fibrosis-4 (FIB-4) index, AST to platelet ratio index (APRI), serum biomarkers like enhanced liver fibrosis (ELF) panel, fibrometer, hepascore etc. But these are not sufficient to detect NASH and its severity and have various limitatations.[2, 15]

Liver biopsy:

This is the gold standard to diagnose the NAFL or NASH and fibrosis but it is controversial to perform biopsy of each patient with suspected NAFLD.[4,14] The important limitations are sampling errors, variability, inter observer difference which may lead to

overestimation or underestimation of disease severity, fibrosis and risk with its complications. This is the only procedure which can distinguish between NAFL & NASH; it can provide prognostic information and can exclude coexisting conditions. Histology shows cellular steatosis,balloon degeneration, inflammatory cell infiltrates, necrosis, Mallory hyaline and fibrosis with its degree. As liver biopsy is an invasive procedure,most of the patients do not prefer the modality and it's not free of risk and complications.[2,4,14]

Management:

Management of NAFLD includes the treatment of liver disease and the associated metabolic disorders like obesity, dyslipidemia, insulin resistance & type 2 diabetes mellitus. The mainstay of NAFLD remains around lifestyle modifications to reduce the body weight and control of risk factors. Although the prevalence of NAFLD is increasing day by day but still now there are no reliable evidence based pharmacotherapy. Several emerging drugs are now in phase 2-3 trials.[1-5]

Life style modifications:

This is the initial approach to treat NAFLD & its advanced forms of the disease which includes weight loss, healthy hypocaloric food intake and physical exercise.[1,2,17]

Diet:

Diet containing refined carbohydrates, sugar-sweetened beverages, excess fructose and saturated fats are rich in calories and are associated with overweight, NAFLD and NASH. Low caloric diets (containing low carbs, low fat, unsaturated fat,omega-3 fatty acid, fibers, specific proteins like fish, poultry and Mediterranean food), intermittent fasting improve NAFLD and NASH.[2,14] Calorie restriction by 30% per day i.e 500-1000 kcal/d appears to be more important to improve the condition than the type of food.[4]Coffee consumption and polyphenol intake may also be useful in the treatment of NAFLD. Caffeine and polyphenols are strong antioxidant that reduce the oxidative stress and inflammation in liver.[2,14] At least three cups of coffee consumption may be recommended to improve NAFLD, NASH and fibrosis.[2] Polyphenols are present in high quantities in vegetables, cereals, fruits, spices etc.

Physical exercise:

Exercise has great beneficial effect on NAFLD, NASH and cardiovascular system irrespective of weight loss. Regular aerobic exercise of moderate intensity like brisk walking, jogging, running, swimming, or cycling etc. (about 150-200 minutes/week) can improve insulin resistance and NAFLD. Higher intensity exercises are required to improve NASH or fibrosis. Exercise also improves sarcopenia, easy fatiguability and quality of life in cirrhotic patients.[2,4]

Weight loss:

Loss of weight for 5 to 10% significantly improves NAFL or steatosis, NASH and liver fibrosis in a dose response relationship i.e 5% weight loss for steatosis, e 7% for NASH, e 10% for fibrosis improvement.[2,4] Sustained weight reduction and maintenance is challenging but effective weight loss can decrease liver injury and improves insulin sensitivity.[2,15]

Bariatric surgery:

It's a therapeutic option which can cure steatosis, NASH, Diabetes and liver fibrosis by increasing significant weight reduction upto 30%. Endoscopic bariatric procedure and metabolic surgery are minimally invasive options for weight loss and are promising in treatment of NAFLD.[1,2,15,18] Current indication for bariatric surgery are severe obesity (BMI e 40kg/m^2) or obesity (BMI e 35 kg/m^2) with other comorbidities like T_2DM, pre-diabetes, uncontrolled hypertension and osteoarthritis of knee or hip joints.[1,2,6] There must be absence of liver cirrhosis or compensated cirrhosis without portal hypertension.[2,6]

Pharmacological treatment:

Till now there are no specific pharmacological drugs approved for the treatment of NAFLD and its other forms. However, different drugs have been investigated during the last decades including few hypoglycemic agents, lipid lowering drugs, antihypertensive and other molecules like obeticholic acid etc.

Summary of important drugs having histological benefits given below in table:

Medications for treatment of NAFLD with their characteristics:[1,2,4]

SI no	Medication with dosage	Mode of action	Indications	Benefits	Adverse effects
1	Vitamin E 800 IU/d	Antioxidant	NASH except T2DM or cirrhosis	Improves Steatosis ? NASH	Risk of stroke (haemorrhagic), Carcinoma prostate
2	Pioglitazone 30-45 mg/d	PPAR- gamma agonist	NASH with or without T_2DM	Improves Steatosis NASH, IR, ? Fibrosis	Weight gain, Risk of heart failure, Carcinoma bladder Bone fracture ,
3	Liraglutide -1.8 mg sc/d in T2DM -0.6 to 3 mg sc/d in obesity	GLP-1 RA	NASH without cirrhosis	Improves steatosis NASH, IR, weight loss, No effect on fibrosis	Gall stone pancreatitis, Anorexia Nausea GI upset
4	Semaglutide 0.4mg sc/d	GLP-1 RA	NASH without cirrhosis	Improves steatosis NASH, IR, weight loss, No effect on fibrosis	Gall stone pancreatitis, Anorexia Nausea GI upset
5	EmpagliflozinDapagliflozin, Canagliflozin	SGLT 2 inhibitor	NAFLD & T2DM	Improves steatosis, ALT level, IR, Modest weight loss	Risk of UTI Hypotension Bone loss
6	Obeticholic acid (Phase III trial)	FXR (FarnesoidX receptor ligand)	NASH, Liver fibrosis	Resolution of NASH, Improves fibrosis	Pruritis Increases LDL Cholesterol
7	Tirzepatide	T2DM	T2DM or Obesity with NAFLD	Improves steatosis, NASH, IR, CV & renal outcome, Prevent stroke	GI upset, Gall stones, Pancreatitis
8	Saroglitazar (PhaseIItrial)	Dual PPAR α/γ agonist	NAFL NASH T2DM	Decrease ALT level, TG,steatosis, NAS, Improve IR	Doubtful effect on fibrosis, Fatigue, GI upset

Above drugs are not approved for management of NAFLD or NASH but can be individualized and prescribed carefullywith comorbidities like T2DM and obesity.[1,2]

Some other drugs:

Metformin does not have any role to reduce liver fat or inflammation but it improves IR. Statins has no beneficial effect on liver histology but it can improve cardiovascular morbidity.Soit can be prescribed in patients with NAFLD with dyslipidemia.[6]Several studies with ursodeoxycholic acid (UDCA) showed that it offers no histological benefit in NASH. According to AASLD guideline metformin, UDCA, statins and silymarin should not be given to treat NASH.[2]

Choice of drugs and duration of treatment:

Drug treatment should be given to patients with NASH with or without liver fibrosis. Choice of drug depends on patient's age, sex, presence or absence of DM, dyslipidemia and other co-morbidities.So it should be individualized considering different factors. Drug efficacy and side effects also will come in consideration. Different scientific societies recommend only vitamin E (800 IU/d) and pioglitazone (30 mg/d) only for treatment of NASH. Suggested duration is two years for both the drugs. INASL recommends saroglitazar (4 mg/d) for one year as treatment of NASH. Assessment of treatment response is also problematic. However, ALT decrease of 17 U/L at 6 months of treatment may be used as improvement.[4]Fibroscan of liver showing CAP and LSM values may also be used to monitor the treatment response.[2, 4, 15]

NAFLD in children and adolescents:

Though initially it was thought that it was a disease of adults but with increasing epidemics of obesity it is increasingly recognized in children and

adolescents.The prevalence in India is about 63% in obese and 12% in non-obese children.[4,19]One study in Bangladesh showed 37.5% NAFLD in obese, 21.15% in overweight and 3.65% in normal weightchildren.[20] Mostly they are asymptomatic. Genetic causes of fatty liver showed also be considered. Detailed discussion about pediatric NAFLD is not possible in this short context. However, lifestyle modification including healthy diet and weight loss is the mainstay of treatment. Vitamin E improves NAFL, NAS & NASH but long-term safety is unknown.[2,4]

NAFLD in lean subjects:

Undoubtedly obesity is a major risk factor for NAFLD but it can also occur in lean individuals (Normal waist circumference and BMI). The prevalence of lean NAFLD is about 4.1% in USA and 19% in Asia.[21] Genetic factors may play an important role in this group. In treatment consideration, weight loss will not be appropriate for them but physical exercise and healthy diet intake may be beneficiary for them.[2,4, 22]

MAFLD, a new term for NAFLD:

Metabolic associated fatty liver disease (MAFLD) is the new nomenclature that had been proposed by a panel of experts instead of NAFLD mainly based on presence of metabolic dysfunctions.[6,19] APASL also supported the new term as because this dysfunction is the key driver of NAFLD.[6] As summary of proposal, MAFLD is diagnosed on presence of hepatic steatosis together with one of three criteria given below: 1) overweight or obesity 2) T2DM 3) clinical evidence of metabolic dysfunction like increased waist circumference and abnormal lipid or glycemic control.[6] In contrary, NAFLD is a heterogeneous disease, only change of nomenclature to MAFLD will not make it homogenous. There is no recognized or accepted criteria for defining metabolic dysfunction.[23, 24] However, there should be more evidence based study to change the name.

Conclusion:

NAFLD is a liver disorder requiring multidisciplinary approach. On initial evaluation possible causes of liver disease and risk factors should be sought out. To identify and early treatment of comorbid conditions like T2DM, dyslipidemia and cardiovascular diseases can significantly improve the prognosis. In spite of many advances in medical sciences there is no approved drug treatment for the disease. Currently lifestyle modifications with weight loss are the only effective treatment for NAFLD.

Conflict of Interest:

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