

Non Alcoholic Fatty Liver Disease (NAFLD) and Type 2 Diabetes Mellitus

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Abstract

Background: The pandemic of obesity and type2-diabetes mellitus has led to a increasing prevalence of Non Alcoholic Fatty Liver Disease (NAFLD) globally, including developing countries. The current epidemic of NAFLD is reshaping the field of hepatology because patients with NAFLD are at increased risk for not only liver-related morbidity and mortality but also cardiovascular disease. NAFLD also increases the risk of developing diabetes. Hence patients with diabetes need to be screened for the presence of NAFLD and vice-versa. It is of paramount importance to differentiate between simple steatosis from Non Alcoholic Steatohepatitis (NASH), the later being more associated with hepatic as well as extra hepatic complications.

Key Words: Diabetes Mellitus; Liver Injury; NAFLD

Abbreviations: NAFLD= Non-Alcoholic Fatty Liver Disease; NASH= Non Alcoholic Steatohepatitis; HCC= Hepatocellular carcinoma;EASL = European Association for the Study of the Liver);AASLD = American Association for the Study of Liver Diseases;EASD = The European Association for the Study of Diabetes);EASO=European Association for the Study of Obesity ; CCL2–CCL5 = C-C chemokine receptor types 2 / type5; FXR = Farnesoid X receptor

INTRODUCTION

NAFLD is a broad spectrum of diseases consisting of patients with simple steatosis or Nonalcoholic fatty liver, Non alcoholic steato hepatitis (NASH), NASH-related cirrhosis, and NASH-related HCC. In NAFL there is $\geq 5\%$ hepatic steatosis without significant inflammation. NASH is defined as steatosis and inflammation associated with the presence of one of the three additional features: ballooning of hepatocytes, Mallory hyaline, and fibrosis on liver histology. NASH is usually a histological diagnosis.

It is very important to differentiate between NAFLD and NASH to determine the prognosis, risk of progression, and for assessing the liver-related and cardiovascular morbidity and mortality, which occurs more frequently in patients with NASH as

compared to simple steatosis.

Why should NAFLD be of interest to diabetologists?

NAFLD is strongly associated with type 2 diabetes mellitus and abdominal obesity.

NAFLD is the hepatic component of metabolic syndrome. The prevalence of NAFLD in diabetes mellitus has been reported to be 74 %¹, 57%² and 70%³ in different studies. As lifestyles have become increasingly sedentary with obesity and type 2 diabetes mellitus pandemic, NAFLD is rapidly becoming the leading cause of chronic liver disease worldwide⁴. It is projected to be the principal etiology for liver transplantation within the next decade.

NAFLD is a risk factor for Type 2 Diabetes mellitus and cardiovascular disease

NAFLD is associated not only with liver-related morbidity and mortality, but also with an increased risk of developing both cardiovascular disease and type 2 diabetes mellitus⁵.

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NAFLD was a significant predictor for future diabetes in a Japanese middle-aged health check population, especially in women. The relative risk of diabetes associated with fatty liver was 4.8 [95% confidence interval (CI) 3.0-7.8, $p < 0.0001$] in men and 14.5 (95% CI 7.0-30.1, $p < 0.0001$) in women⁶. Current evidence shows that with resolution of fatty liver, there is a potential for decreasing risk of incident type 2 diabetes mellitus⁷.

NAFLD is also significantly associated with a moderately increased cardiovascular disease risk among type 2 diabetic patients. This risk is independent of other classical risk factors and only partly explained by the presence of metabolic syndrome (8). In fact, patients with NAFLD are twice as likely to die of cardiovascular disease than liver disease and liver disease is only the third leading cause of death in patients with NAFLD, following cardiovascular disease and malignancy⁹.

Type 2 Diabetes increases the risk of NAFLD progressions to more advanced liver disease

Type 2 diabetes mellitus is one of the strongest clinical predictors of the progression of NAFLD to NASH and cirrhosis (10). The progression of NAFLD to NASH in non-diabetic individuals occurs in about 10-20 % of NAFLD patients¹¹. But the presence of Type 2 diabetes increases this risk of the progression by two- to three-fold¹². The presence of diabetes also increased the risk for cirrhosis or hepatocellular carcinoma (HCC) among patients with NAFLD/NASH. In fact Type 2 diabetes has emerged as a significant predictor of worse outcomes in patients with NAFLD/NASH¹³. There are data to demonstrate that HCC may occur in NAFLD patients without cirrhosis^{14,15}. These data emphasize the need to effectively diagnose NAFLD and early HCC in patients with obesity, metabolic syndrome and type 2 diabetes mellitus.

Diagnosis of NAFLD

The diagnostic criteria of NAFLD includes hepatic steatosis by either imaging or histology, no other causes of steatosis and no significant alcohol

consumption.¹⁶

All individuals with metabolic risk factors should be screened with ultrasonography of the liver to identify liver fat and assessment of liver enzymes. However, ultrasonography is a relatively insensitive technique for detecting liver fat. The fatty infiltration must be at least 20–30%, before ultrasonography will be able to diagnose hepatic steatosis. As an alternative, a simpler surrogate markers for diagnosing liver fat, such as the fatty liver index (a composite score derived from BMI, waist circumference, fasting triacylglycerol and γ -glutamyltransferase [GGT] concentrations) can be used as a first-line approach that also has an acceptable sensitivity and specificity for identifying liver fat¹⁷.

For diagnosis of NAFLD, other causes of steatosis should be excluded including but not limited to increased alcohol consumption, viral hepatitis, surgical procedures, use of medications and total parenteral nutrition. There is a disagreement among different guidelines in defining the threshold for alcohol intake. According to EASL¹⁷, significant alcohol consumption is defined as > 30 g/d in men and > 20 g/d in women. The AASLD guidance considers¹⁸ > 21 standard drink per week in men and > 14 in women as significant. Asia-Pacific Guidelines¹⁹ defines significant alcohol intake as > 7 standard alcoholic drinks/week (70 g ethanol) in women and > 14 (140 g) in men.

Components of the metabolic syndrome and diabetes should be screened. After making a diagnosis of NAFLD, the next step is assessment of fibrosis as the severity of fibrosis is the strongest predictor of liver-related outcome.

Although histological examination of the liver is the 'gold standard' to stage NAFLD severity, it is not a feasible option due to invasiveness of the test, complications, cost involved, and poor acceptability of the patients. Hence the use of non-invasive test for detection of liver fibrosis is recommended which includes NAFLD fibrosis score, Enhanced

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Liver Fibrosis [ELF] or FIB-4 scores.

Depending on the results of these tests either follow-up at 3–5 years or specialist referral for a decision as to whether to undertake a liver biopsy, and/or initiation of therapy. Alternatively, for NAFLD patients with mild abnormalities of non-invasive fibrosis markers, further follow-up at 2 years with repeat testing is advocated ²⁰. The EASL–EASD–EASO guidelines recommend that all patients with elevated LFTs because of NAFLD and advanced fibrosis should be referred to a hepatologist ²⁰.

Role of liver biopsy

Liver biopsy should be reserved for the following conditions. NAFLD patients who are at increased risk of having steato hepatitis and/or advanced fibrosis and in patients with suspected NAFLD in whom competing etiologies for hepatic steatosis and the presence and/or severity of coexisting CLDs cannot be excluded without a liver biopsy ¹⁸.

Treatment

Lifestyle changes: Lifestyle modification including diet, exercise, and weight loss has been recommended for treatment of patients with

NAFLD. The recommendation is to give 500-1000 kcal energy deficit diet to induce a weight loss of 500-1000 g/week with a 7%-10% total weight loss. Dietary recommendation also involves exclusion of NAFLD-promoting components (processed food, and food and beverages high in added fructose. Weight loss has been reported to be associated with improvement in histologic features. 150-200 min/week of moderate intensity aerobic physical activities in 3-5 sessions are generally preferred (brisk walking, stationery cycling)¹⁷. However, lifestyle modification is difficult to achieve and to sustain

Pharmacological treatment

Whom to treat?

Drug therapy is indicated for progressive NASH (bridging fibrosis and cirrhosis) and early-stage NASH with increased risk of fibrosis progression (age >50 years; diabetes, MetS, increased ALT or active NASH with high necroinflammatory activity ¹⁷.

The recommendation of drug therapy for the treatment of NAFLD by different society are summarized in table 1.

Table 1.

Drugs	EASL	ASIA-PACIFIC	AASLD
Metformin	Insufficient evidence	Not beneficial	Not beneficial
Vitamin E	Insufficient evidence	Not beneficial	Consider use in non-diabetic, biopsy-proven NASH
PPAR-gamma agonists	Consider use in selected diabetic patients	Insufficient evidence in Asian	Pioglitazone indicated in biopsy-proven NASH (regardless of diabetes)
UDCA	Not beneficial	Not mentioned	Not beneficial
Silymarin	Not mentioned	Insufficient evidence, potentially useful	Not mentioned
Statins	Safe but not beneficial	Safe but not beneficial	Safe but not beneficial

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Future pharmacological options of NASH Gut microbiome

NAFLD is associated with increased gut permeability and transportation of gut metabolites and bacterial products into the portal circulation.

An increased lipopolysaccharide levels in the circulation occurs, which binds to the monocyte differentiation antigen (CD14)-TLR-4 complex triggering an inflammatory reaction and insulin resistance. The gut microbiota is also involved in choline metabolism by converting it into toxic dimethylamine and trimethylamine, which are transported to liver and converted into trimethylamine oxide (TMAO) that causes liver inflammation and damage²¹.

Changing the gut microbiota may be a treatment option in NAFLD. Solithromycin, a macrolide antibiotic with anti-inflammatory properties, was found to improve NASH in animal studies and is currently being studied in a phase 2 clinical trial²².

Antiobesity medications

Orlistat is a gut lipase inhibitor which decreases the absorption of dietary fats. A small pilot study demonstrated reduction in hepatic steatosis associated with Orlistat-induced weight loss²³. However, it is not currently recommended as a treatment for NAFLD, but can be prescribed as an adjunct medication to help with weight loss in the NAFLD patients²⁴.

Peroxisome proliferator-activator receptors (PPARs)

PPARs are nuclear receptors that bind fatty acids and fatty acid derivatives to regulate a number of metabolic processes. The three PPAR agonist considered for use in NAFLD are Elafibranor (dual PPAR α/δ agonist) Pioglitazone (PPAR γ agonist), and Saroglitazar (dual PPAR α/γ agonist).

Elafibranor has been shown to improve peripheral tissue insulin sensitivity and reduce alanine aminotransferase (ALT) levels in patients with metabolic syndrome²⁵. A phase 3 trial using

elafibrinor versus placebo for 72 weeks is currently ongoing for the treatment of NASH. (NCT02704403).

PPAR γ agonists like thiazolidinediones are used in the treatment of diabetes and demonstrated to be effective in NASH²⁶. However, undesirable side effects and the possible need for long-term therapy have limited widespread acceptance.

Saroglitazar is a dual PPAR α/γ agonists which combines the beneficial effects of activating both PPAR receptors. It has been shown to improve diabetic dyslipidemia²⁷ and is currently approved in India for this indication. A retrospective study of NAFLD patients with dyslipidemia treated with saroglitazar for 24 weeks demonstrated a significant decrease in ALT compared with baseline²⁸. A phase 3 trial is currently ongoing in India to assess the effect of saroglitazar versus placebo for 52 weeks in biopsy proven noncirrhotic NASH (Clinical Trials Registry-India CTRI/2015/10/006236).

Farnesoid X receptor agonist

Bile acids can negatively regulate bile acid synthesis, decrease hepatic gluconeogenesis, and lipogenesis through interaction with their intracellular receptor, the farnesoid X receptor (FXR).

A synthetic bile acid agonist of FXR, obeticholic acid (OCA) was evaluated in a phase 2b clinical trial (FLINT) which included biopsy-proven noncirrhotic NASH patients who were randomized to OCA 25 mg/day versus placebo for 72 weeks²⁹. This important study established the role of FXR in NASH by showing that the FXR bile acid agonist OCA improved histological features of NASH. Histological improvement, with no worsening of fibrosis was demonstrated in a significant study participants on OCA as compared to placebo (45% vs 21%, $P = 0.0002$). and decrease in fibrosis score was also significant. A phase 3 trial to compare the effectiveness of OCA versus placebo for noncirrhotic biopsy-proven NASH is currently ongoing (NCT02548351).

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Incretins, dipeptidyl peptidase-4 inhibitors and sodium–glucose cotransporter 2 inhibitors.

Glucagon-like peptide GLP-1 receptor agonists or incretin mimetics, liraglutide was investigated in a phase 2 trial for its effectiveness in biopsy proven NASH³⁰. This important study (LEAN trial) established the utility of GLP-1 pathway in NASH by demonstrating that the long-acting GLP-1 analogue, liraglutide, led to histological resolution of NASH. The primary end point of histological resolution of NASH without worsening of fibrosis was reached by 39% of study participants on liraglutide versus 9% on placebo (P = 0.02).

Cenicriviroc

Cenicriviroc is an oral antagonist of the CCL2–CCL5 receptor, A phase 2b trial (CENTAUR) is investigating the effect of 2 years of cenicriviroc or placebo on noncirrhotic NASH and liver fibrosis in patients with T2DM or metabolic syndrome (NCT02217475). Interim analysis at year 1 of the CENTAUR study, showed significant improvement in fibrosis and no worsening of steatohepatitis as compared to placebo³¹.

CONCLUSION

NASH is become a leading cause for chronic liver disease worldwide due to the pandemic of diabetes mellitus and obesity. NAFLD and especially NASH also confer an independent risk of adverse cardiovascular events in affected individuals beyond that conferred by the shared risk factors. Hence differentiation of simple steatosis from NASH is of paramount importance along with the staging of fibrosis of liver.

Currently, a number of drugs are undergoing pivotal trials as potential therapy for NASH. The first effective drug to be approved for treatment of NASH is anticipated to be available by 2020.

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