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REVIEW PAPER

A BIRD'S EYE VIEW OF NON ALCOHOLIC FATTY LIVER DISEASE - AN INSULIN RESISTANT STATE

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ABSTRACT

Nonalcoholic fatty liver disease (NAFLD) is an increasingly recognized form of chronic liver disease. It encompasses a spectrum of conditions associated with lipid deposition in hepatocytes. It ranges from steatosis (simple fatty liver), to nonalcoholic steatohepatitis (NASH—fatty changes with inflammation and hepatocellular injury or fibrosis), to advanced fibrosis and cirrhosis. Studies have suggested that although simple fatty liver is a benign condition, NASH may progress to fibrosis and lead to end-stage liver disease. The disease is mostly silent and often discovered through incidentally elevated liver enzyme levels. It is strongly associated with obesity and insulin resistance and is currently considered by many as the hepatic component of the metabolic syndrome. NASH cirrhosis is now one of the leading indications for liver transplantation particularly in the United States. As NAFLD is considered to be one of the insulin resistant states like Type 2 Diabetes Mellitus (T2M) a brief understanding of the disease is essential in regions where obesity and T2M are prevalent in the majority of the population. Therefore the present review outlines the salient features of NAFLD.

Keywords: *steatosis, steatohepatitis, nonalcoholic fatty liver disease(NAFLD), non alcoholic steatohepatitis (NASH), insulin resistance, type 2 diabetes mellitus*

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD), which includes nonalcoholic steatosis and nonalcoholic steato-hepatitis (NASH), describes the clinicopathologic spectrum of alcohol-like liver disease in the nonalcoholic.[1]

Although it may be observed as an iatrogenic complication (due to drugs or anti-obesity surgery) or secondary to various other conditions (toxins, lipodystrophic syndromes, hypobetalipoproteinemia), NAFLD most commonly occurs as a primary (idiopathic) disease. The clinical importance of primary NAFLD appears to rest on three main observations:

- *It commonly occurs in the general population worldwide and among patients presenting with unexplained mild to moderate raised aminotransferase levels .*
- *It is not a sign or symptom of disease but it is a pathological condition that has the potential to progress to advanced hepatic and extrahepatic disease, and to interact with other etiologies of liver disease .*
- *It may recur following orthotopic liver transplantation and poses a heavy burden of complications in the setting of major extrahepatic and liver-related surgery .*

REPORTED RISK FACTORS

The conventional risk factors for the development of primary NAFLD include type II diabetes, insulin resistance, hyperlipidemia and obesity.[2] NAFLD typically

Table 1. *List of conditions associated with macrovesicular steatosis of liver*

Conditions Associated With Macrovesicular Steatosis
Nonalcoholic fatty liver disease
Alcohol
Drugs—estrogens, coumadin, tamoxifen, valproic acid, methotrexate, isoniazid, corticosteroids, vitamin A, troglitazone, l-asparaginase, amiodarone, perhexiline, calcium channel blockers, nucleoside analogues
Hepatitis C (genotype 3)
Nutritional factors—rapid weight loss, total parenteral nutrition
Surgical considerations—gastrointestinal surgery for obesity, extensive small-bowel resection
Metabolic disorders—cystic fibrosis, abetalipoproteinemia, others
Syndromes associated with obesity, insulin resistance—lipodystrophies, hypopituitarism, Prader-Willi syndrome

affects 50% of diabetics and 76% of obese patients,[3,4] and is the most common of all liver diseases. However, the prevalence of NASH is substantially less, affecting 18.5% of obese patients.

Other traditional risk factors include hyperuricemia, central obesity defined as waist circumference greater than 100 cm in males and greater than 88 cm in females, and hypertension.

Secondary causes of NAFLD include nutrition-related complications, such as total parenteral nutrition, rapid weight loss, and intestinal jejuno-ileal bypass surgery. Common causes of steatosis are listed in table 1.

Certain drugs are associated with NAFLD. Metabolic syndromes and pregnancy-related fatty liver diseases are also some of the secondary causes of NAFLD. Patients with normal body mass index (BMI) may develop NAFLD even in the absence of traditional risk factors. It is thought that the primary abnormality may be occult insulin resistance or central adiposity.[5]

The natural history of NAFLD still remains poorly defined. Mortality among NAFLD patients is greater than age and sex-matched controls.[6] Because of features of the metabolic syndrome, these patients are at high risk for cardiac-related death. Still liver disease is the third most common cause of mortality in this population.[6] Clinical predictors of more advanced disease include people with diabetes, hypertriglyceridemia[7] and those older than 40 years of age. Table 2 outlines the diagnostic criteria for metabolic syndrome.

DIAGNOSIS

Majority of the patients with NAFLD are asymptomatic or suffer from nonspecific symptoms and signs such as fatigue, malaise or right upper quadrant pain. Serum aspartate aminotransferase and alanine aminotransferase levels are modestly elevated, although the ratio of aspartate aminotransferase to alanine aminotransferase is less than one, distinguishing NAFLD patients from those with alcohol-induced liver disease.[8]

The International Federation of Clinical Chemistry and Laboratory Medicine established in 2002 a reference system for the measurement of enzyme activity of clinically important enzymes, including ALT, to be measured at 37 °C.[23] Levels of 10-45 U/l are considered as normal, although reference values may still vary among laboratories. The degree of elevation of transaminases does not reflect the underlying severity of the disease. The diagnosis of NAFLD can be suspected on the basis of radiological imaging such as ultrasound or magnetic resonance imaging.

However, the sensitivity of these modalities is low and often there is a significant degree of inter observer variability. A minimum of 30% of hepatocytes needs to be infiltrated by steatosis for the imaging techniques to detect fatty liver.[9]

Currently, the only method of distinguishing simple steatosis from NASH is the liver biopsy. Brunt et al[10] proposed a grading and staging system for NASH. Grade 1 reveals mild steatosis, predominantly macrovesicular with minimal ballooning of hepatocytes and minimal inflammation. Grade 2 shows moderate steatosis, usually mixed macrovesicular and microvesicular with ballooning present in zone 3 hepatocytes, and some lobular inflammation. Grade 3 shows all the features of grade 2 plus the additional requirement of portal inflammation. Staging requires the presence of Masson trichrome stain. Stage 1 reveals zone 3 perivenular, perisinusoidal fibrosis, either focal or extensive. Stage 2 requires the features of stage 1, plus focal or extensive portal fibrosis. Stage 3, shows bridging fibrosis and stage 4 reveals cirrhosis with or without perisinusoidal fibrosis.

PATHOGENESIS

The progression from simple steatosis to steatohepatitis, fibrosis and cirrhosis is thought to be a two-hit hypothesis.

Table 2. *Diagnostic criteria for the metabolic syndrome: presence of two or more of the following parameters*

Parameter	Value
Impaired glucose tolerance	Fasting blood glucose level ≥110 mg/dL *(5.6 mmol/l)*
High blood pressure	≥130/85 mm Hg
Elevated triglyceride levels	>250 mg/dL *(1.7 mmol/l)*
Low high-density lipoprotein level	<40 mg/dl (1 mmol/l) for men; <50 mg/dl (1.3 mmol/l) for women
Abdominal obesity	Waist: >102 cm (40 inches) for men; >88 cm (35 inches) for women

First hit

The first hit results in fat accumulation within the liver parenchyma. This occurs in abnormalities during uptake, synthesis and secretion of lipids resulting primarily from insulin resistance, which is quite common in patients with NAFLD.[11] Insulin resistance is often a primary abnormality in patients with NAFLD. There is often a genetic predisposition to insulin resistance, even in the absence of frank diabetes. Twenty per cent of the nondiabetic population may exhibit insulin resistance. Patients that exhibit more pronounced levels of insulin resistance exhibit a greater degree of steatosis.[12] Central adiposity may contribute to the flow of excess free fatty acids (FFAs) to the liver by providing a direct route through the portal vein.[13] Patients with NAFLD often have risk factors such as type II diabetes, hyperlipidemia, hypertension and obesity, which are part of the insulin resistance syndrome. Hyperinsulinemia promotes lipolysis in the adipocyte, resulting in increased FFAs delivered to the liver. In the hepatocyte, FFAs stimulate synthesis of more FFAs and inhibit oxidation of FFAs.[14] Insulin sensitivity is also influenced by peptide mediators, otherwise known as adipocytokines, such as tumour necrosis factor alpha (TNF-α), leptin and adiponectin. TNF-α influences steatosis by stimulating the release of FFAs from adipocytes into the liver.

TNF-α may directly induce apoptosis of hepatocytes promoting activation of hepatic stellate cells, stimulating fibrosis.[15] Leptin (Leptin resistance which is considered to be one of the possible third hit hypothesis) potentially may stimulate platelet-derived growth factor, ultimately leading to hepatic stellate cell proliferation resulting in fibrosis.[16] Adiponectin may have a protective role against fatty liver. Recently it was shown that adiponectin levels were significantly reduced in patients with NAFLD compared with controls resulting in an inverse relationship between insulin resistance and adiponectin levels.[17] This observation may result in a future therapeutic role for adiponectin in the pharmacological management of NAFLD.

Second hit

The second hit is hepatocellular injury that results from oxidative stress, lipid peroxidation and direct cellular toxicity from FFAs.[18] Multiple mechanisms regarding hepatocyte injury have been proposed:

1. Increased expression of cytochrome P450 isoform CYP2E1 has been shown to occur in patients with NASH. CYP2E1 is a pro-oxidant, resulting in increased production of reactive oxygen species, capable of peroxidizing cell membranes.

2. Increased insulin levels and insulin resistance (IR) leads to peripheral lipolysis resulting in excess fatty acids being oxidized in peroxisomes. Oxidation, along with binding and export of fatty acids, is the primary method of protecting the liver from subsequent damage.(Fig.1)

3. The peroxisome proliferators activated receptor-alpha (PPAR-α) is responsible for regulating the esterification and export of fatty acids in very low density lipoprotein, in the binding of fatty acids and in mitochondrial and peroxisomal oxidation. Reduced expression of PPAR-α may have an important role in the pathogenesis of NASH.[19]

4. Mitochondrial abnormalities have been described in patients with NASH, but not in those with simple steatosis. These mitochondrial abnormalities lead to increased mitochondrial fatty acids beta-oxidation, eventually resulting in free radical formation, hepatocyte injury and steatohepatitis.[20]

METHODS OF MANAGING THE DISEASE

Lifestyle modification, primarily targeting weight loss achieved through dietary modification and exercise

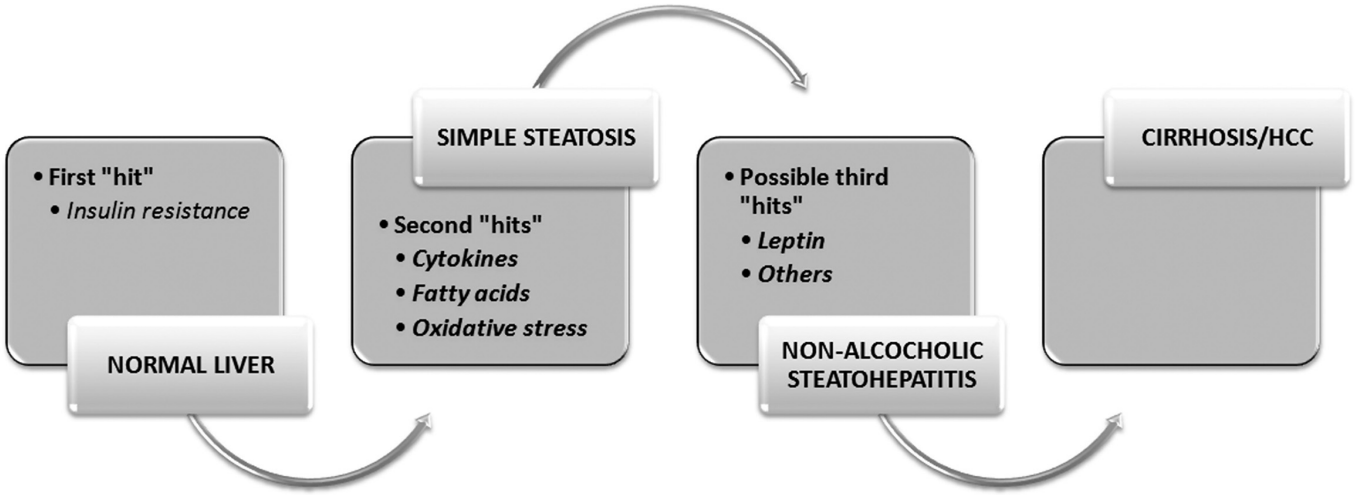

Figure 1. *Pathogenesis of non-alcocholic fatty liver disease: the "multiple hit" hypothesis. HCC - hepatocellular carcinoma*

form the current basis of management. Additionally, treatment of all other aspects of the metabolic syndrome must be instituted. Weight loss and exercise both improve insulin resistance,[21] which theoretically should improve steatosis. Weight loss should not exceed more than 1 kg per week, because rapid weight loss can exacerbate steatosis. Similarly very low calorie diets that give less than 500 kcal/day and jejunoileal bypass surgery should be avoided as a method of weight loss, due to the risk of worsening fibrosis. The recommended target for weight loss is 10% of a person's body weight over a six-month period.[22]

DRUGS TO INDUCE WEIGHT LOSS

One case study indicated that orlistat treatment in patients with NASH was safe, and did show significant histological improvement in both degree of steatohepatitis and fibrosis say after six to 12 months of therapy.[24] Orlistat is a reversible inhibitor of gastric and pancreatic lipase, and is one of two agents that have been approved for the management of obesity. This drug forms a covalent bond with the active serine residue of gastric and pancreatic lipase in the stomach and small bowel, blocking the digestion and absorption of dietary triglycerides. Orlistat in combination with a controlled energy diet, rather than diet alone, significantly increased weight loss in obese adults after one year of therapy.[25]

The second approved drug in the management of obesity is sibutramine and also evaluated in patients with NASH.[26] Sibutramine in combination with a low calorie diet-induced weight loss improved insulin resistance and transaminases, as shown by ultrasonographic regression in fatty liver, compared with diet alone. It is a noradrenaline-serotonin reuptake inhibitor and produces weight loss by a dual mechanism: reduction of food intake and increase in energy expenditure. Average weight loss is in the range of 5% to 8% from baseline. Recently, rimonabant, a selective cannabinoid-1 receptor blocker, has been shown to improve cardiovascular risk factor profile and reduce body weight.[27]

Certainly, diet should be combined with exercise to initiate and maintain weight loss. Exercise will enhance calorie deficit necessary for weight loss.[28]

PHARMACOTHERAPY FOR NAFLD

Currently, there are no approved pharmacological options for the treatment of NAFLD. Only three randomized controlled trials have been conducted to evaluate the efficacy of medical treatment in NAFLD (Table 3). The agents studied include antioxidants with vitamins E and C in combination, ursodeoxycholic acid and metformin. The remaining trials performed to date have been observational in design, had small sample size, and have had a short follow-up period. Other druges like the thiazolidinediones are a class of insulin-sensitizing agents used to treat type II diabetes were tried in NASH patients with toxic side effects.[29]

CONCLUSIONS

Obesity epidemic is a global phenomena carrying with the risk of precipitating insulin resistant states including NAFLD which is shown to be on the rise. The primary abnormality for NAFLD reported is that of intrinsic insulin resistance. There seems to be no approved pharmacological therapies for the treatment of NASH. Diet and Exercise and aggressive risk factor control are the major suggested remedies for NAFLD and NASH.

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