

Chapter 70

Non-Alcoholic Fatty Liver Disease — An Epidemic of the New Millennium

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) represents a spectrum of conditions characterized by macrovesicular hepatic steatosis in the absence of significant alcohol intake (less than 20 gm/day for males and 10 gm/day for females). Two main histological patterns are recognized: 1. Steatosis without inflammation; and 2. steatohepatitis (NASH) with inflammation, fibrosis and cirrhosis. NAFLD is also divided into two types. Primary NAFLD refers to fatty liver associated with metabolic syndrome (obesity, type 2 diabetes, hyperlipidemia and insulin resistance). On the other hand, secondary NAFLD includes fatty liver disease with a proximate cause (Table 1).

EPIDEMIOLOGY

Description of liver disease resembling NAFLD has been reported under various names as far back as the 1950's e.g. obesity related liver disease, nutritional cirrhosis, diabetic hepatitis or non-alcoholic diabetic cirrhosis. Ludwig, et al¹ at the Mayo Clinic first described a histopathological pattern of "steatohepatitis" in middle aged diabetic women in 1980. This entity received little attention till the mid-nineties because of a bias among clinicians that fatty liver was a benign condition with little clinical significance. This perception has undergone a sea change with a large number of publications relating to NAFLD since 1995.

Current estimates of prevalence of NAFLD vary widely according to the population studied and the diagnostic criteria used, e.g. imaging, abnormal liver function test or liver biopsy. Based on ultrasound findings the prevalence ranges from 10-51% with a

Table 1: Types of NAFLD

Primary	Secondary
1. Insulin resistance	1. Severe weight loss
a. Obesity	a. Jejunioileal bypass
b. Diabetes	b. Gastric bypass
c. Hypertriglyceridemia	c. Severe starvation
d. Hypertension	
	2. Total parenteral nutrition
	3. Iatrogenic
	a. Amiodarone
	b. Diltiazem
	c. Tamoxifen
	d. Steroids
	e. Highly active antiretroviral therapy
	4. Refeeding syndrome
	5. Toxic exposure
	a. Environmental
	b. Workplace
	6. Disorders of lipid metabolism
	a. Abetalipoproteinemia
	b. Hypobetalipoproteinemia
	c. Andersen's disease
	d. Weber-Christian syndrome

consensus figure of 20 to 30% for most populations². An Indian study reported a prevalence rate of 24.6% with a preponderance of males³. Studies using abnormal transaminase levels for diagnosis showed a lower prevalence rate, although when abnormal GGT was included, the prevalence went up to 24%⁴. Among living donors, the prevalence of NAFLD based on liver biopsy varies widely from 33-88% and the prevalence of moderate to severe steatosis ranged from 5-41%⁵.

The prevalence of NASH is between 5.7 and 17% in the general population⁶. More worrying, however, is a

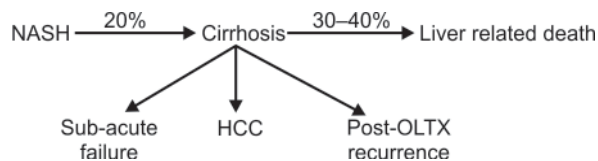


Fig. 1: Natural history and clinical outcomes of NASH

review of studies highlighting the fact that fibrosis or even cirrhosis was present in 15-50% of patients with NASH on their index biopsy, suggesting progressive liver disease in these patients (Fig. 1).

NAFLD is more common in males and occurs in all age groups although the highest prevalence is in those between 40 and 49 years. The prevalence increases with increasing body weight and 70-80% obese individuals have NAFLD. The rate of obesity in NAFLD patients has been reported to be from 30 to 90%. The prevalence of NASH also increases to 15-20% in morbidly obese subjects. NAFLD is also independently associated with type 2 diabetes (30-55%), hyperlipidemia (20-60%), hypertension and insulin resistance as well as globally with the presence of metabolic syndrome. The relative importance of each of these factors is difficult to determine since they often co-exist.

In India, NAFLD occurs at a lower BMI as compared to the western population and a BMI of 22 kg/m² is considered critical for development of NAFLD³. Indians have higher body fat percentage and adverse pattern of fat distribution including central obesity even when BMI is within limits. Thus, measures of central obesity and waist:hip ratio is considered a better risk factor for NAFLD in Indians. NAFLD occurs at a younger age in Indians, but a majority have only mild inflammation (Type 1/2) which is a relatively milder disease compared to Type 3/4 which progresses to cirrhosis in 25-40% patients⁷.

There is evidence of increasing obesity and diabetes worldwide. In the US, diabetes has increased more than 50% since 1980 and obesity is estimated at 30% of the population. In India, the diabetic population is estimated to rise from its current level of 30 million to 57 million by 2025. India is also facing an obesity crisis among the neo-wealthy middle class especially in the urban population where obesity prevalence has been shown to be as high as 30%. Although large follow up studies are not available, but a Japanese study based on ultrasound showed an increase in prevalence of NAFLD from 12.6% in 1989 to 28.4% in 2000⁸. Given the rapid rise of obesity, diabetes and related conditions worldwide, the NAFLD is likely to increase in parallel and assume an epidemic proportion.

NATURAL HISTORY

Evidence shows that NAFLD is not a benign disease as commonly perceived.

Survival in NAFLD patients followed up for 23.5 years was significantly lower than in the general population. The occurrence of cirrhosis, overall death and liver related death were 5%, 12.6% and 17% respectively⁹. The presence of impaired fasting glucose/diabetes, older age or cirrhosis were independent risk factors associated with a poorer prognosis.

The natural history of NAFLD depends critically on the disease stage. Patients with simple steatosis have a relatively benign prognosis with a risk of developing cirrhosis over 15-20 years in the order of 1-2%, whereas 12% patients with NASH and fibrosis may progress to cirrhosis over 8 years¹⁰.

Studies have shown a similar proportion of sex distribution and features of metabolic syndrome such as diabetes mellitus or obesity in patients with NASH and cryptogenic cirrhosis, which is different in other causes of cirrhosis¹¹. The patients with NASH, however, were younger than patients with cryptogenic cirrhosis by about 10 years. This suggests that NASH may indeed be the likely cause of cryptogenic cirrhosis. It is being increasingly recognized that most cases of cryptogenic cirrhosis may represent 'burnt-out' NASH, although this issue has been difficult to address because NASH related cirrhosis appears to lose the characteristic histological features when end-stage liver disease develops. Thus, the frequency of progression to end-stage liver disease may be underestimated in cohort studies of NASH patients.

PATHOPHYSIOLOGY

A strong association between NAFLD and metabolic syndrome supports insulin resistance as a pathogenic mechanism for NAFLD. The "two hit" hypothesis explains the pathogenesis by the first "hit" – steatosis— which sensitizes the liver to a variety of second "hits" which lead to necro-inflammation and fibrosis. Lipase mediated metabolism of free fatty acids (FFA) in liver is inhibited due to high insulin level in patients with insulin resistance. Thus, FFA accumulate in liver cells and overwhelm the mitochondrial oxidative capacity leading to fat accumulation.

The adipocytes are not only an inert storage depot for energy substrate, but are active as an endocrine organ producing a variety of cytokines including leptin, resistin, angiotensinogen, TNF alpha, FFA etc which have a proinflammatory role. It has been shown that

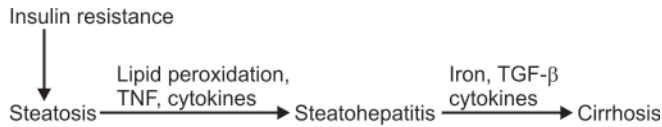


Fig. 2: Pathogenesis of non-alcoholic fatty liver disease

patients with NASH are more insulin resistant than fatty liver alone. This raises the possibility that insulin resistance may be a "second" as well as a "first hit. Lipid peroxidation and oxidative stress appear to play a major role in inflammation (Fig. 2). Hepatic cytochrome P-450 expression is increased in patients with NAFLD. Increased expression of this enzyme leads to increased lipid peroxidation, resulting in increased oxidative stress and inflammation. Cytokine expression may result from free radicals released as a result of lipid peroxidation. Increased hepatic expression of tumor necrosis factor may be found.

Increased iron and ferritin in NAFLD may activate stellate cells to produce collagen. Another potential contributor to hepatic steatosis and inflammation is bacterial overgrowth which increases hepatic oxidative stress.

Prevalence of NAFLD varies among different racial groups which suggest that genetics also plays a role.

CLINICAL FEATURES AND DIAGNOSIS

Most patients with NAFLD are asymptomatic whilst others have non-specific symptoms such as fatigue or RUQ discomfort. A diagnosis of NAFLD should be considered in the following scenarios (i) a symptomatic elevation of transaminase not due to viral hepatitis or excess alcohol; (ii) patients with features of metabolic syndrome; and (iii) incidentally detected fatty liver on ultrasound. Besides, it should also be considered in the differential diagnosis of cryptogenic cirrhosis.

Clinical examination in patients with NAFLD is usually unremarkable except for hepatomegaly which is present in 50%. Patients with stigmata of chronic liver disease may be present in advanced disease.

Liver function abnormalities are primarily restricted to mild elevation of transaminases (<5 X upper limit of normal) which may be present in 50-90% of hospital based population of NASH patients. Although the SGPT levels are higher than SGOT, but the converse may be an indicator of fibrosis or cirrhosis. The transaminase values do not correlate with the degree steatosis or fibrosis. Alkaline phosphatase levels may be modestly elevated (< 2 X upper limit of normal) in 40-70% of patients. Serum ferritin is elevated in 20-50% patients

and raised transferrin saturation may be present in 5-10% patients. This may cause confusion with a diagnosis of hemochromatosis. Serum auto antibodies (anti-nuclear and anti smooth muscle) are present in 23-36% of NAFLD patients and although the significance of this observation is unclear, it may rarely signal co-existent auto-immune liver disease.

Ultrasound has a high sensitivity (60-94%) and specificity (88-95%) for diagnosis of fatty liver (with more than 30% fat infiltration) and has been most commonly used in clinical practice because it is relatively inexpensive. With a non-contrast CT scan, hepatic steatosis has a low attenuation and appears darker than the spleen. CT scan also has high sensitivity for diagnosis and may be useful when semi-quantitative assessment is required or when multiple comparative studies are planned. Both magnetic resonance phase contrast techniques and magnetic resonance spectroscopy are reliable at detecting steatosis and offer good correlation with hepatic fat volume. The routine application of MRI, however, is limited by cost and lack of availability.

Despite the usefulness of the imaging modalities, none of these modalities can distinguish between fatty liver versus steatohepatitis. Thus, liver biopsy remains the only accurate way to diagnose steatohepatitis.

The gold standard for diagnosing NAFLD is clinicopathological correlation with confirmation of steatosis by liver biopsy and exclusion of other etiologies, e.g. alcohol (a limit of 20 gm/day of alcohol for women and 30 gm/day for men is commonly used to distinguish between alcoholic and non-alcoholic fatty liver, although in the Indian context the limit should be lower by 10 gm in both sexes). Secondary causes such as drugs should be excluded as NAFLD due to these conditions has a different course and treatment.

In general, for clinical utility the diagnosis can be made with some confidence in patients who have increased transaminase level, no other cause of liver disease and ultrasound finding of increased liver echogenicity consistent with fatty infiltration. The issue is whether liver biopsy is needed in all cases to confirm the diagnosis of NASH. Liver biopsy is the only way to distinguish between simple steatosis and NASH and is the best modality for grading and staging of disease which is crucial for prognosis and patient management. Alternatively, hepatic steatosis without NASH is quite common and performing a liver biopsy in all patients would appear to be over-aggressive, particularly in the absence of a treatment of proven benefit. The arguments are further complicated by the description of a spectrum of NAFLD patients with normal serum transaminase

levels. Thus despite its poor acceptability, cost and associated small risk of complications, liver biopsy is required to confirm the diagnosis of NASH. It is indicated in patients with a high probability of NASH or in those where the diagnosis is uncertain. Certain features such as obesity, type 2 diabetes mellitus, age > 45 years and a SGOT/SGPT ratio > 1 are suggestive of higher risk of NASH and biopsy should be considered in these patients.

TREATMENT

There is no standard recommended treatment for NAFLD. In the absence of treatment modalities of proven efficacy, therapy is directed towards correction of risk factors. The various treatment modalities are shown in Table 2.

Although randomized control trials are not available, lifestyle modification and weight loss have been recommended in practice guidelines. Reports of weight loss through diet and exercise have shown improvement in transaminase level and liver histology¹². The target of weight loss should be 10% of base line weight and should proceed at about 0.5 kg per week. Very rapid weight loss can worsen steatohepatitis and increase the risk of gallstone disease. Current recommendations call for at least 30 minutes of physical activities such as brisk walking daily. Diet remains an important component of weight loss regimen. Saturated fats in the diet worsen insulin resistance whereas dietary fiber can improve insulin resistance.

Pharmacological agents used to reduce body weight have also been shown to be effective in treatment of NASH. In small trials, Orlistat and Sibutramine given for 6 months led to significant weight loss and improvement in steatosis and fibrosis¹³. Bariatric surgery is

another option for patients with morbid obesity and NASH.

Free radicals damage organelles and stimulate cellular injury and fibrosis. Antioxidants (by inhibiting lipid peroxidation) and cytoprotective agents (by stabilizing cellular and organelle phospholipids membrane) have been extensively studied for treating NASH. Vitamin E 400-1200 IU/d has been shown to improve liver function and in combination with Vitamin C 1 gm/day has also shown improvement in fibrosis score¹⁴. Ursodeoxycholic acid (UDCA) has also been extensively studied. In a dose of 10-15 mg /kg, it improves hepatic enzymes and decreases hepatic steatosis. A recent large randomized double-blind placebo-controlled study showed significant improvement in biochemistry and histology although a similar improvement also occurred in the placebo group¹⁵. The efficacy of UDCA has been confirmed in many uncontrolled trials but larger studies are warranted. Betaine has also found to be an effective therapy in small trials. Another new therapy that is advocated is pentoxifylline, a drug that has been used successfully in alcoholic hepatitis¹⁶.

Considering the importance of insulin resistance in disease pathogenesis, drugs improving insulin resistance e.g. metformin and thiazolidinediones have been evaluated for treatment of NAFLD. Metformin (850 mg bid) given over 6-12 month period has been shown to improve transaminase levels and necroinflammatory activity in a number of trials¹⁷. Studies with Pioglitazone and Rosiglitazone have also shown promising results in treatment studies¹⁸. Thiazolidinediones tend to induce weight gain, which may clearly be an important drawback of prolonged treatment.

In absence of a definite treatment, the first step in management of NAFLD should be lifestyle modification and weight loss in the overweight, optimal management of diabetes and avoidance of alcohol.

UDCA and vitamin are commonly used but long term studies are lacking. Other treatments, including pharmacological treatment of insulin resistance in the non-diabetic, appears promising but requires further studies.

Table 2: Treatment of NAFLD

Nonpharmacologic therapy
Diet
Exercise
Pharmacologic therapy
Ursodeoxycholic acid
Lipid lowering agents
Metformin
Thiazolidinediones
Betaine
Vitamin E
Pentoxifylline

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