Non-Alcoholic Fatty Liver Disease (NAFLD)

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is a broad term encompassing a spectrum of abnormalities of the liver. The incidence of NAFLD is rapidly rising and so is the available knowledge and information regarding it. NAFLD is emerging as a common cause of liver dysfunction in non-alcoholics. It is found to be associated with multiple conditions like obesity, diabetes mellitus, hyperlipidaemia, etc. Basic pathogenesis includes fat deposition in hepatocytes with varying degree of inflammation and regeneration of the liver. Presentation of NAFLD varies from asymptomatic to florid liver cell failure in advanced cases of NASH (non-alcoholic steatohepatitis). The disease is mainly diagnosed by exclusion of other conditions with a high index of suspicion for NAFLD. There is no specific management available for NAFLD; early diagnosis and treatment of the underlying condition remains the mainstay of treatment. However, there is much scope for research to let us understand the disease and deal with it appropriately. Non-alcoholic fatty liver disease (NAFLD) is a common cause of chronic liver disease and its incidence is rising worldwide. Understanding its pathogenesis, biochemical parameters, histological grading and staging, and its management, are vital issues today in clinical practice.

Keywords: Obesity, Insulin resistance, Hyperlipidaemia.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a common cause of chronic liver disease and its incidence is rising worldwide. Understanding its pathogenesis, biochemical parameters, histological grading and staging, and its management, are vital issues today in clinical practice.

The term NAFLD is used to describe a wide spectrum of fatty liver changes ranging from fatty liver and steatosis on one side, to non-alcoholic steatohepatitis (NASH) and cirrhosis on the other.

Before diagnostic tests for hepatitis C were available, cases of NAFLD were diagnosed wrongly as non-A, non-B hepatitis. Now after such tests for hepatitis C and E are available, NAFLD is more accurately defined. Initially it was thought to be an mild disease with little clinical significance, but at present NAFLD is recognised as a major cause of cryptogenic cirrhosis of liver.

Definition

As the term suggests, NAFLD is deposition of fat in the liver of a non-alcoholic subject, a condition which may progress to end-stage liver disease. The spectrum of progression of NAFLD is similar to alcoholic liver disease, but is not caused by chronic alcohol consumption. The spectrum of pathological changes described in NAFLD consists of 4 types (Table I). The clinical implications of NAFLD are of significance as it occurs in the general population and may progress to cirrhosis of liver and liver cell failure.

Table I: Pathological changes in NAFLD.

<table>
<thead>
<tr>
<th>Type</th>
<th>Pathological Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Only fat deposition</td>
</tr>
<tr>
<td>II</td>
<td>Fat deposition + inflammation</td>
</tr>
<tr>
<td>III</td>
<td>Type I + advanced inflammation and ballooning degeneration</td>
</tr>
<tr>
<td>IV</td>
<td>Type I + fibrosis and/or Mallory bodies and cirrhotic changes</td>
</tr>
</tbody>
</table>

Prevalence

NAFLD is an extremely common liver disease in the United States (USA) affecting approximately 20% of the adult population. In different countries, its prevalence is 10 - 24% of the general population. Amongst the obese persons, the prevalence rises to 57 - 74% and 25 - 75% amongst obese diabetics. Accordingly, NASH can be considered as the 3rd commonest cause of liver disease after hepatitis C and alcohol abuse in the US.

Investigators in their studies found that once chronic alcohol ingestion, viral, drug-induced, autoimmune and metabolic...
causes such as Wilson’s disease and haemochromatosis were ruled out, virtually all the remaining patients were proved to have NAFLD.

In India, data regarding NAFLD is lacking, but with increasing awareness and understanding about this disease, a gradually rising trend is seen.

**NAFLD and associated conditions**

NAFLD is associated with various conditions, which may be considered while diagnosing it. It is mainly associated with:

- **Obesity** (69 - 100%)
- **Diabetes mellitus** (36 - 75%)
- **Hyperlipidaemia** (20 - 81%)

These conditions are associated with insulin resistance and metabolic syndrome, which is frequently observed with NAFLD.

**Obesity**: More than 70% of patients with NASH are obese. Body weight ranging from 10 - 40% higher than ideal is associated with 4 - 6 fold higher incidence of NAFLD. There is direct correlation between the severity of obesity and severity of NAFLD.

**Diabetes**: Upto 75% patients with NASH have diabetes mellitus. Obese, middle-aged females with DM are more likely to have fatty liver changes on ultrasonography (upto 70%).

**Hyperlipidaemia**: 20 - 80% of patients with NASH have hyperlipidaemia in the form of high blood cholesterol level and/or high triglyceride levels.

Other associated conditions:

- Total parenteral nutrition for prolonged periods.
- Severe insulin resistance.
- Significant and rapid weight loss in obese subjects.
- Familial lipid disorders, e.g., αβ-lipoproteinaemia, hypolipoproteinaemia.
- Limb lipodystrophy.
- Weber-Christian disease.
- Drugs: corticosteroids, methotrexate, tamoxifen, diltiazem, nifedipine, tetracyclins, penicillin, synthetic oestrogen, etc.
- Occupational exposure to toxins such as hydrocarbons.
- Surgical procedures: jeuno-ileal bypass, gastropexy, biliopancreatic bypass, extensive loss of small intestines during surgery, post liver transplantation.

**Human immunodeficiency virus (HIV) and NAFLD**: NAFLD has been reported in acquired immunodeficiency syndrome (AIDS) patients. HIV itself, or nucleoside analogues, (e.g., Nevirapine, Stavudine, etc.) used in its treatment, DM, obesity, etc., also contribute towards the initiation and progression of NAFLD.

**Pathogenesis and natural history**

Pathogenesis in NAFLD is characterised by fat deposition, inflammation, and fibrosis of liver.

**Fat deposition**: macrovesicular fat deposition occurs in the liver.

**Inflammation**: steatohepatitis results as a consequence of multiple factors – chiefly, insulin resistance leading to accumulation of free fatty acids; and other mechanisms like oxidative stress, lipid peroxidation, endotoxins, iron overload, etc. Various cytokines, like tumor necrosis factor (TNF) and interleukins (IL-6, IL-8) are responsible for inflammation. TNF affects mainly the triglyceride synthesis in the liver.

**Fibrosis**: steatohepatitis progresses to increasing fibrosis and later on cirrhosis may develop. About 12% of patients with NAFLD may progress to cirrhosis within 7 years. Cirrhosis secondary to NASH may progress to hepatocellular carcinoma.

**Predictors of NASH and advanced fibrosis**:

**HAIR score**

1. Hypertension
2. Alanine transaminase (ALT) > 40 IU/l
3. Insulin resistance (IR) index > 5

Presence of 2 or all 3 factors predict NASH.
BAAT score

1. Body mass index (BMI) > 28 kg/m²
2. Age > 50 yrs
3. ALT > 2-fold rise
4. TG > 1.7 mmol/l

Presence of none or only 1 factor rules out the possibility of fibrosis or cirrhosis.

Clinical features

Most patients of NAFLD (45 - 100%) have no symptoms or signs of liver disease at the time of diagnosis. In these patients, abnormal liver function tests are often discovered incidentally.

When symptoms occur, they are non-specific – like persistent fatigue (50 – 73%), pruritus (0 – 6%), oedema (2 – 10%), malaise, and right upper quadrant discomfort or pain.

Other features like GI bleeding (0 – 3%), jaundice (0 – 5%), ascites (0 – 3%), pruritus, and oedema point towards severe liver disease. Ascites, hepatic encephalopathy, and variceal bleeding indicate cirrhosis of liver due to progressive NASH.

When the disease is not advanced, diffuse non-tender smooth hepatomegaly is present in 25 – 53% of patients. Such patients are usually obese and/or diabetic. Advanced disease may present with right hypochondrium tenderness, jaundice, palmar erythema, spider angioma, portal hypertension, ascites, varices, and splenomegaly.

Diagnosis

Diagnosis of NAFLD is one of exclusion of other causes of liver dysfunction. Thus one needs to ascertain the absence of alcohol abuse, viral, autoimmune, metabolic, hereditary or other known causes of liver pathology before keeping the diagnosis of NAFLD. Generally, absence of alcohol abuse or consumption of alcohol of < 20 g/day for prolonged periods, and negative serological tests for hepatitis B and C should raise the suspicion of NAFLD (Table II).

### Table II: Approach to diagnosis of NAFLD

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification of NASH</td>
<td>Rule out alcoholism</td>
</tr>
<tr>
<td>Raised ALT in high-risk groups</td>
<td>History of hepatotoxicity</td>
</tr>
<tr>
<td>Fatty liver on imaging</td>
<td>Reassess renal function and electrolyte imbalance</td>
</tr>
<tr>
<td>Elevated serum transaminases, alkaline, etc.</td>
<td>ALT, AST, alkaline phosphatase, etc.</td>
</tr>
<tr>
<td>Liver biopsy (diagnostic and staging of the disease)</td>
<td>Biopsy diagnosis of advanced fibrosis</td>
</tr>
</tbody>
</table>

Diagnosis by biochemical parameters: (Table III).

### Table III: Biochemical parameters

<table>
<thead>
<tr>
<th>Lab Parameter</th>
<th>Abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT, AST</td>
<td>&gt; 4-5 fold increase</td>
</tr>
<tr>
<td>ADAMTS6</td>
<td>Usual&lt;10 fold increase, &lt;2 fold increase</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>2-3 fold increase</td>
</tr>
<tr>
<td>GGT</td>
<td>Usual&lt;2 fold increase</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>&gt; 0.5 mg/dl, &gt; 3 fold increase</td>
</tr>
<tr>
<td>Albumin</td>
<td>&gt; 0.5 mg/dl, &gt; 3 fold increase</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>&gt; 30 sec</td>
</tr>
<tr>
<td>Serum iron saturation</td>
<td>&gt; 20%</td>
</tr>
<tr>
<td>Transferrin</td>
<td>&gt; 20%</td>
</tr>
<tr>
<td>Ferritin</td>
<td>&gt; 20%</td>
</tr>
<tr>
<td>Transaminases</td>
<td>&gt; 20%</td>
</tr>
<tr>
<td>Transaminases</td>
<td>&gt; 20%</td>
</tr>
<tr>
<td>Lipoamidase</td>
<td>&gt; 20%</td>
</tr>
</tbody>
</table>

Diagnosis of NAFLD by imaging: Non-invasive radiological imaging studies such as USG, CT scan of abdomen, and MRI may help in diagnosis of fatty infiltration of liver; but they do not distinguish between fatty liver, steatohepatitis and steatohepatitis with fibrosis – for which liver biopsy is required.

a. USG findings in NAFLD:
   - Increased echogenicity (hyperechogenic) liver.
   - Increased liver contrast compared to kidney.
   - Vascular blurring – mainly of hepatic veins.
- Attenuation of echogenic level in deep-seated areas.

USG examination is to be performed first as it is the least expensive and carries no risk of radiation. Its sensitivity is more, but it lacks specificity.

b. CT scan findings in NAFLD:
- Focal areas of fatty infiltration may be picked up.
- Mean CT Hounsfield unit in liver less than that in spleen helps in diagnosis.

It is a costly technique, sensitivity is comparable to USG, but specificity is more than that of USG.

c. MRI findings in NAFLD:
- Fatty infiltration of liver correlates very well to phase contrast imaging giving very good quantitative assessment of disease status.
- Useful for excluding fatty infiltration.
- On T1-weighted images, there is loss of intensity in the focal areas of fat deposition. So, early stage of disease with small lesions are readily identified on MRI.

It is more sensitive and specific compared to USG or CT scan, but considerably more expensive.

d. Radionuclide scanning (scintigraphy) studies:
- With technetium-99m sulphur colloid scanning, focal areas of fat deposition are identified as filling defects.
- Radio-xenon has a very high affinity for fat and it remains bound to and retained in fat. This provides qualitative as well as quantitative assessment of fat deposition in liver.

e. Laparoscopy:

It provides a direct view of the liver for macroscopic pathological changes. It shows scattered yellow spots on the surface of liver, when > 30% of it is involved and there is no fibrosis. Diffuse yellow appearance is seen when similar fatty changes are present with fibrosis of the liver. This difference may be accentuated by use of a dye – indocyanine green.

### Histological diagnosis by liver biopsy:

After exclusion of other liver diseases, diagnosis of NAFLD can only be ascertained by a liver biopsy. It is the most sensitive and specific investigation, also necessary for staging, typing, and explaining prognosis of the disease.

On histological examination, the findings of NAFLD are very much similar to those of alcoholic liver disease. Determination of hepatic iron store is an important parameter in distinguishing NAFLD from haemochromatosis. Degree of rise in ferritin level is much high in haemochromatosis than in NAFLD.

The histopathological changes in NASH include hepatic steatosis, ballooning degeneration, acute, chronic or mixed inflammation, perisinusoidal fibrosis, and Mallory hyaline bodies.

Burnt et al. have described fibrotic changes in NASH in 4 stages (Table IV).

<table>
<thead>
<tr>
<th>Stage</th>
<th>Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Zone III perisinusoidal or pericellular fibrosis, either focal or diffuse</td>
</tr>
<tr>
<td>II</td>
<td>Stage I + extensive periportal fibrosis</td>
</tr>
<tr>
<td>III</td>
<td>Stage II + focal or extensive bridging fibrosis</td>
</tr>
<tr>
<td>IV</td>
<td>Cirrhosis of liver</td>
</tr>
</tbody>
</table>

Table V compares the histological findings in NASH and alcoholic liver disease (ALD).

<table>
<thead>
<tr>
<th>Comparative histology in NASH and alcoholic hepatitis</th>
<th>Alcoholic hepatitis (%)</th>
<th>NASH (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe steatosis</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Lobular hepatitis</td>
<td>54</td>
<td>85</td>
</tr>
<tr>
<td>Periportal fibrosis</td>
<td>0</td>
<td>33</td>
</tr>
<tr>
<td>Mallory bodies</td>
<td>3</td>
<td>16</td>
</tr>
<tr>
<td>Fibrosis/cirrhosis</td>
<td>38</td>
<td>63</td>
</tr>
<tr>
<td>Nuclear vacuolation</td>
<td>76</td>
<td>7</td>
</tr>
<tr>
<td>Bile duct proliferation</td>
<td>53</td>
<td>96</td>
</tr>
</tbody>
</table>
Management options for NAFLD

No established treatment is available for NAFLD. Some empiric treatment strategies have been suggested.

**General measures:** Gradual weight loss is advised in obese and overweight subjects. It results in improvement in laboratory abnormalities and steatosis. More than 10% patients will show normalisation of elevated ALT levels and decrease in hepatomegaly. Rapid or abrupt weight loss (> 1.6 kg/wk) is not advocated as it may lead to progression of NAFLD. Weight loss should not be complete either. Gastrojejunal bypass surgery for obesity and long-term parenteral nutrition therapy should be avoided as far as possible.

**Dietary management:** diet should have restriction in rapidly absorbed carbohydrates like monosaccharides and disaccharides. High protein diet with high protein-calorie is also helpful.

**Management of associated conditions:**

- **Diabetes mellitus:** patients with DM should have proper control of blood sugar. Insulin resistance is associated so insulin sensitizers like metformin and pioglitazone may be added in therapy. Metformin also has anorexiant action and helps in weight loss. However, there is no definite study carried out for the use of these agents in NAFLD; the suggestion is logical.

- **Hyperlipidaemia:** dietary fat restriction and lipid lowering drugs are helpful in this condition. Mainly drugs causing decrease in triglyceride levels are helpful. Drugs like gemfibrozil, clofibrate, and statin group of drugs are indicated. But it is to be kept in mind that fibrates may cause drug-induced hepatitis in some patients.

- **Certain drugs:** are associated with development of NAFLD as described earlier. They should be discontinued and other proper alternatives should be substituted.

- **Metronidazole:** in a dose of 750 - 2,000 mg per day for 3 months is shown to resolve steatohepatitis associated with jejunal bypass surgery. This therapy needs evaluation for use in other types of NAFLD.

- **Calorie-free amino acid infusions:** have reversed steatohepatitis associated with jejunal ileal bypass, but this is not assessed in cases of NAFLD.

**Drugs used in management of NAFLD:** drugs used to reduce insulin resistance and triglyceride levels have already been described above. Certain drugs called ‘hepatoprotective drugs’; like ursodiol (ursodeoxycholic acid) 13 - 15 mg/kg/d, vitamin E 400 - 1,200 mg/d, betaine 20 g/d, N-acetyl cysteine 1 g/d are also used. Lastly, role of antioxidants is also investigated extensively as accumulation of lipid peroxidation products in response to free radical injury leads to oxidative stress which is important in causing liver cell injury.

Hence, antioxidants like vitamin E, beta-carotene, vitamin C, lecithin, etc., may be tried. Vitamin E is shown to decrease liver enzymes significantly. Betaine and other methylated amino acids act as methyl group donors and decrease fat uptake and there by fat accumulation in liver cells. Betaine is a promising drug.

Ursodeoxycholic acid (UDCA) in a dose of 13 - 15 mg/kg/d for one year has been found to improve ALT and steatosis in patients with NAFLD. It acts by its cytoprotective, immunomodulatory, chemoprotective, and antioxidant properties. UDCA is cytoprotective as it has high lipid altering property. It stabilises the hepatocyte membrane and prevents cell membrane injury. It also improves cell injury in liver. It helps in preservation of mitochondrial function which in turn reduces steatosis because of clearance of fat accumulation in liver. Early treatment is the best option to prevent further progression of NAFLD and to reverse the changes to near normal.

**Conclusion**

NAFLD is an important common cause of chronic liver disease and cryptogenic cirrhosis of liver associated with insulin resistance. Its incidence is reportedly on the rise the world over. Realising its significance, there is now greater understanding of its aetiology, pathogenesis and management. Early diagnosis and early management is of vital importance. Early treatment with UDCA and antioxidants has been advocated. However, effective treatment options are still lacking for which future stepwise work is required by research workers.
References


4. Sheh S et al. NAFLD, study to determine whether AST/ALT ratio may be used as an index to distinguish NASH. Annals of Internal Medicine 1997; 126: 137-45.


6. Tsai FC, Gunfield C et al. The fatty liver in AIDS. Seminar Gastrointestinal Disease 2002; 13 (9): 47-64.


