Fatty liver: A risk factor for chronic liver disease and new strategy for its management
Rashid MH, Haque MA, Alam MS, Sarker MK, Hossain MMI

Introduction
The liver occupies a central position in lipid metabolism. A small, rapidly used pool of fatty acids (FFAs) absorbed from the diet or released into the blood from chylomicrons or fat cells, accommodates almost all of the energy requirements of a fasting animal. Free fatty acids are taken up by the liver to join hepatic pool of free fatty acid a portion of which the liver synthesizes. Some Free fatty acids are oxidized to CO₂ in the liver for energy, but most are rapidly incorporated into complex lipids (phospholipids, triglycerides, glycolipids, cholesterol esters etc.). Some of these complex lipids enter a slowly used pool that comprises the structural lipids of liver cells and their storage site. Most triglycerides enter an active pool where they combine with specific apoproteins to form lipoproteins (e.g. VLDL), which are secreted into plasma. The liver is also responsible for lipid degradation. Fatty liver occurs when lipid accumulation exceeds.

Accumulation of fat largely triglycerides within liver parenchyma exceeds 5% of the liver weight is defined as fatty liver. It is caused by the failure of normal hepatic fat metabolism either due to a defect within the hepatocytes or to delivery of excess fat, fatty acid or carbohydrate beyond the secretory capacity for lipid of the liver cells. Fatty liver disease can range from fatty liver alone to fatty liver associated with inflammation (steatohepatitis). This condition can occur with the use of alcohol (alcohol related fatty liver) or in the absence of alcohol (NAFLD).

Figure 1: Normal liver

Fatty liver associated with alcohol may occur with as little as 10 oz of alcohol ingested per week. Identical lesion can be caused by the other diseases or toxins.

Types
Aetiological:
1. Alcoholic Fatty Liver Disease (AFLD)
2. Non Alcoholic Fatty Liver Disease (NAFLD)

Morphological:
1. Microvesicular
2. Macrovesicular

www.orion-group.net/journals
www.orion-group.net/medicaljournal
Pathophysiology
Proposed mechanism of fatty liver disease:
- Increased delivery of dietary fat or fatty acid to the liver.
- Increased mitochondrial synthesis of fatty acids or reduced oxidation.
- Impaired export of triglyceride out of the liver cell.
- Excess carbohydrate delivery to the liver.

Non alcoholic fatty liver disease (NAFLD)
These papers mainly focus on non alcoholic fatty liver disease (NAFLD). NAFLD Ranges from nonalcoholic hepatic steatosis to nonalcoholic steatohepatitis (NASH). A large body of literature clearly indicates that NAFLD is strongly associated with the metabolic syndrome. Early studies identified obesity and diabetes as the two major risk factors for the development of NAFLD1. It is known that hypertriglyceridemia and hypertension are also frequently present in subjects with NAFLD. The metabolic syndrome is characterized by constellation of findings including obesity, diabetes, hypertension and hypertriglyceridemia, principal risk factors for NAFLD2 (Table-01).

Metabolic syndrome (Table-01) (ATP III recommendations)8

<table>
<thead>
<tr>
<th>Component</th>
<th>Defining level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose intolerance</td>
<td>Fasting glucose ≥6.1mmol/l or known type 2 DM.</td>
</tr>
<tr>
<td>Central obesity</td>
<td>Waist circumference &gt;102cm for men &amp; &gt;88cm for women.</td>
</tr>
<tr>
<td>Hypertension</td>
<td>≥130/85mm Hg or on treatment.</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>Fasting triglyceride ≥1.7 mmol/l or current use of fibrate.</td>
</tr>
<tr>
<td>Low HDL cholesterol</td>
<td>&lt;1.0 mmol/l for men, &lt;1.3 mmol/l for women.</td>
</tr>
</tbody>
</table>

[Metabolic syndrome is defined by the presence of three or more of these features HDL, high-density lipoprotein; ATP; adult treatment panel]

Insulin resistance syndrome (Table-02)

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Diabetes Mellitus, glucose intolerance or hyperinsulinemia and two or more of the following.</td>
<td>140/90 mm of Hg or current documented use of antihypertensive medications.</td>
</tr>
<tr>
<td>2. Hypertension</td>
<td>140/90 mm of Hg or current documented use of antihypertensive medications.</td>
</tr>
<tr>
<td>3. Elevated triglycerides and/or decreased HDL lipoprotein levels.</td>
<td>TG &gt;1.7 mmol/l.</td>
</tr>
<tr>
<td>4. Central (truncal) obesity</td>
<td>Waist/hip ratio &gt; 0.9 for men and &gt; 0.85 for women.</td>
</tr>
<tr>
<td>5. Microalbuminuria</td>
<td>Urinary albumin excretion rate of 20 mg/min.</td>
</tr>
</tbody>
</table>

Epidemiology
- 10-39% of the global population affected.
- 20% of average incidence.
- 50% of diabetics.

www.orion-group.net/journals
www.orion-group.net/medicaljournal
57-74% of obese persons.
90% of morbidly obese persons.
It is the 2nd most common diagnosis after chronic viral hepatitis in USA.
In USA over 30 million adults have NAFLD; of these 8.6 million have NASH.
NASH is a major contributor of cryptogenic cirrhosis.

Aetiology
Common:
- Obesity
- Type II Diabetes Mellitus
- Hyperlipidaemia
- Medications
- Associated with insulin resistance syndrome and metabolic syndrome.

Others:
- Intestinal bypass
- Starvation
- Total parenteral nutrition
- Galactosemia
- Systemic disease
- Malnutrition
- Rapid weight loss
- Wilson's disease
- Fever
- Cryptogenic

Medications known to cause fatty liver:
- Glucocorticoids
- Aspirin
- Tamoxifen
- Tetracycline
- Cocaine
- Didanosine
- Bleomycin
- Calcium-channel blocker
- Synthetic estrogens
- Barium salts
- Methotrexate
- Valproic acid
- Zidovudine
- Antimony
- Coumadin

Pathogenesis of steatohepatitis (NASH)

Two hit theory:
First hit: First hit is the steatosis i.e. accumulation of fat within liver cell.
Second hit: Fat deposition followed by oxidative stress, cytokines that produce inflammation & cell damage.
Mechanism of free fatty acid toxicity
- Membrane disruption (detergent effect) at very high concentration.
- Inhibition of $\text{Na}^+ / \text{K}^+$ ATPase.
- Inhibition of glycolysis.
- Uncoupling of mitochondrial beta-oxidation.
- Overall disruption of mitochondrial function.
- Dysregulation of intracellular calcium homeostasis.

Predictors of fibrosis in NASH

**Body mass index over 30:**
- 45 or more years of age.
- AST: ALT ratio greater than 1.
- Type-2 diabetes mellitus.

**In those with BMI over 35:**
- ALT $>$ 40 U/L
- Hypertension
- Insulin resistance

**Clinical features**
- Asymptomatic.
  - Raised ALT.
  - USG finding of bright echogenic liver.
- Pain or discomfort in right hypochondrium.
- Smooth hepatomegaly.
- Features of underlying diseases.

**Diseases should be excluded**
- Alcoholic liver diseases.
- Chronic hepatitis B.
- Chronic hepatitis C.
- Hypothyroidism.
- Autoimmune liver diseases.
- Wilson's diseases.
- Haemochromatosis.

**Investigations**
- LFT.
- Blood sugar.
- Lipid profile.
- HBV marker.
- HCV marker.
- Thyroid function test.
- USG of hepatobiliary system.
- CT scan of liver.
- Laparoscopy, Biopsy.

---

**Figure 5:** Pathogenesis of nonalcoholic steatohepatitis (NASH)

**Figure 6:** USG of fatty liver disease

**Figure 7:** CT scan of fatty liver
Histopathologic findings of NASH
- Steatosis.
- Hepatocyte ballooning degeneration.
- Intrahepatic inflammation.
- Perivenular & perisinusoidal collagen deposition.
- Mallory's hyaline body.
- Bridging septa.
- Cirrhosis.

Figure 8: Laparoscopic view of fatty liver

Figure 9: Histopathologic findings of NASH

Grading & staging of NASH

Grading:
- Grade 1: Mild
  Steatosis: Predominantly macrovesicular ranges from 33-66% of the lobules.
- Grade 2: Moderate
  Steatosis: Any degree usually mixed macrovesicular & microvesicular.
- Grade 3: Severe. (florid steatohepatitis)
  Steatosis: Mixed (Usually 66%).

Staging:
- Stage 1: Zone 3 Perivenular, perisinusoidal or pericellular focal or extensive fibrosis.
- Stage 2: Stage 1 plus focal or extensive portal fibrosis.
- Stage 3: Bridging fibrosis, focal or extensive.
- Stage 4: Cirrhosis with or without residual perisinusoidal fibrosis.

Differentiation of NASH from Alcoholic Steatohepatitis (ASH)
i. History.
ii. AST/ALT ratio: AST/ALT ratio >2 in ASH.

Management
- **Weight reduction**: (I) 0.5 kg/week for children. (II) 1.6 kg/week for adult (not rapidly).

- **Good control of diabetes, hyperlipidaemia**: - For DM insulin sensitizer drug: Metformin, Pioglitazone, Rociglitazone. For hyperlipidaemia: Fibrates, Statins.

- **For obesity**: - Orlistat.

- **Use of cytoprotective drugs**: - UDCA, Antioxidant, S-adenosylmethionine, Salimarine, Pentoxyphyline.

- **Liver transplantation**

Figure 10: Management strategy for patient presenting with suspected non-alcoholic fatty liver disease. It is

www.orion-group.net/journals
www.orion-group.net/medicaljournal
assumed that these patients have had other causes of abnormal liver blood tests excluded by history (for alcohol excess and hepatotoxic drugs) and serology (for autoimmune disease and viral hepatitis) and have steatosis detected on abdominal ultrasound. ACE, angiotensin converting enzyme; HCC, hepatocellular carcinoma; RCT, randomized controlled trials; T2DM, type 2 diabetes mellitus; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; HCC, hepatocellular carcinoma.

Conclusion
At present there is no established therapy for NAFLD based on evidence from large RCTs. Treatment for all patients whatever the severity of their disease, should therefore be directed at the associated risk factors: obesity, type 2 DM, hyperlipidemia and hypertension. This strategy will reduce morbidity and mortality may also be beneficial to the liver. Patient with one or more risk factors for advanced NAFLD should probably undergo liver biopsy to determine their disease stage. Patients with advanced fibrotic disease should be followed up and enter surveillance programs for varices and HCC. For the future studies in animal models of NAFLD and pilot studies in humans have reported encouraging data for a variety of novel treatment strategies based on our increasing understanding of disease pathogenesis. It is hoped that within the next few years results from currently on going large clinical trials of these strategies will provide a firm evidence base for the use of safe, well tolerated life style modifications and/or pharmaceutical agents with beneficial effects on liver histology, currently the best available surrogate marker for long term prognosis.15.

References
Review Article


