Fatty Liver: Is it Benign?

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Abstract
Fatty liver is a common hepatic condition, which is characterized by accumulation of lipids within the hepatocytes. Two major histological patterns, microvesicular and macrovesicular steatosis have been identified. Microvesicular steatosis presents acutely and is associated with a grave prognosis. Mitochondrial dysfunction due to a variety of causes result in its typical manifestations. Macrovesicular steatosis is much more common and associated with chronic conditions. Alcohol remains the commonest cause in the developed world. It is now believed that macrovesicular steatosis is a part of a continuum of illness, which consists of non-alcoholic steatohepatitis, fibrosis and finally cirrhosis. This progressive nature has been documented in follow up studies. Risk factors like diabetes and obesity seem to predict progression to fibrosis. Therefore, fatty liver can no longer be considered benign but regarded as a precursor to fibrosis and cirrhosis.

Introduction
Steatosis of the liver or "fatty liver" is a common sonographic and histological finding. It denotes the excessive accumulation of lipids within the hepatocytes. By definition, this quantity should either be the accumulation of lipids more than 5% of liver weight or visualization of fat globules in more than 5% of hepatocytes. Therefore the equivocal diagnosis of fatty liver is dependant on histology and quantification of the liver tissue rather than clinical and biochemical parameters. Using this definition, autopsy studies have estimated the prevalence of fatty liver of 12-33%. 1,2

The fat globules seen on histological sections generally contain triglycerides. However, cholesterol esters accumulate in Wolman’s disease, sphingolipids in Gaucher’s and Niemann-Pick disease, and phospholipid accumulation is seen in drug toxicity due to amiodarone and perhexilene maleate. Unlike triglyceride deposition which is restricted to the hepatocytes, the other lipids also accumulate in the Kupffer cells.3

Fatty change represents an imbalance in synthesis and secretion of lipids. However, the varied aetiopathogenesis suggests multiple mechanisms. Disruption in delivery of fatty acids to the liver, increased endogenous synthesis, impaired oxidation, deficient export mechanisms and impaired lipolysis have been implicated as pathogenetic mechanisms in fatty liver.

Pathology
Diffuse fatty infiltration of the liver results in a soft liver. On gross examination, the liver appears pale yellow with a greasy, smooth surface. The normal liver is estimated to contain approximately 5 gm of lipid per 100 gm wet weight, of which triacylglycerol (TAG) contributes 20%, phospholipids 53% and unesterified cholesterol 8%. 4 In contrast, in fatty liver, the total lipid may constitute up to 50% of the liver weight, of which TAG contributes 55-70%.4
Microscopically, the distribution of fatty acid droplets may vary depending on the etiology of steatosis. Diabetes, obesity and alcohol related fatty change seems to predominate in Zone 3; whereas in malnutrition, the steatosis is more in acinar Zone 1. Two patterns of fatty liver are recognized: macrovesicular and microvesicular (Figure 1). This pattern of histological change forms a useful framework to classify causes of hepatic steatoses (Tables 1 & 2).  

![Macrovesicular Steatosis - Microvesicular Steatosis](image)

**Fig. 1: Patterns of Fat Accumulation**

**Table 1: Causes of Macrovesicular Steatosis**

- Alcohol
- Obesity
- Non-insulin dependant diabetes mellitus
- Cachexia and malnutrition: Kwashiorkor, Starvation, Choline deficiency
- Total parenteral nutrition
- Intestinal bypass
- Drugs: Corticosteroids, Tamoxifen, Amiodarone, Chloroquine, Oestrogens, Nifedipine, Diltiazem, Methyldopa, CC14.
- Hepatitis C
- AIDS
- Hepatic adenoma
- Hepatic ischaemia

Evidence from animal and human alcoholic subjects suggests that the patterns of lipid deposition may represent sequential stages in the evolution of hepatic steatosis. Initially, the accumulation of fat occurs in the endoplasmic reticulum and in the Golgi apparatus giving the appearance of microvesicles. Ultimately, these vesicles coalesce...
breach the membrane barrier and become macrovesicles. The pattern of steatosis is largely dependent on time. Depending on the time course of the underlying pathology, both patterns of change can even coexist in the same liver.

### Table 2: Causes of Microvesicular Steatosis

- Acute fatty liver of pregnancy
- Reye’s syndrome
- Alcoholic foamy degeneration
- Drugs and Toxins: Amiodarone, Dilantin, Tetracycline, Valproic acid, Fluorouracil, Salicylate
- Congenital & Metabolic: Urea cycle enzyme deficiency, Defects in fatty acid oxidation, Lysosomal acid lipase deficiency
- Miscellaneous: Fulminant hepatitis D, Fatal exertional heat stroke, Toxic shock syndrome, Hepatic ischaemia, Wolman’s disease

### Macrovesicular Steatosis

As can be expected form the proposed sequence of lipid accumulation, macrovesicular steatosis occurs in long standing liver disease conditions (Table 1). In the developed world, alcohol abuse is the commonest cause of fatty liver. The main factor is excessive delivery of fatty acids to the liver. In cases of acute alcohol ingestion, the source is from hydrolysis of triglycerides in the adipose tissue. The prime mover in this situation is believed to be epinephrine. On the other hand, with chronic alcohol abuse, increased synthesis of fatty acids and decreased degradation are the possible pathogenetic mechanisms.

Fatty change is the commonest histological finding in a patient with alcohol abuse and has a reported incidence between 10 and 90%. Fatty liver is also common in obese patients with a reported frequency ranging from 60-90%, with women more affected. In general, the degree of steatosis correlates with the severity of obesity.

The prevalence of fatty liver in diabetics varies between 30-80%. It is most common in non-insulin dependant diabetes mellitus (NIDDM) than the insulin dependant diabetes mellitus (IDDM). The confounding factor is that many of these subjects are also obese. Conversely, majority of obese people with fatty liver have abnormal glucose metabolism. The severity of fatty liver in diabetics correlates with the degree of obesity as well. It is therefore likely that obesity is the major factor in the development of fatty liver.

Other prominent causes of fatty liver include nutritional disorders, particularly kwashiorkor. The mechanism for fat accumulation is believed to be due to an imbalance in hepatic carbohydrate, protein and lipid metabolism. Bacterial overgrowth and production of endotoxin, which results in mitochondrial damage by lipid peroxidation, is another proposed mechanism. Total parenteral nutrition results in abnormalities in liver function tests and on occasion fatty infiltration. Fatty liver is common after ingestion of large caloric loads for a prolonged period of time. Interestingly, the presence of lipid in the infused nutrients does not correlate with the development of fatty liver. In patients with jejunoileal bypass for morbid obesity, maximum fatty infiltration occurs in the first six months after surgery with gradual return to preoperative levels by two years. Protein calorie malnutrition that occurs in the rapid weight loss phase and decreased amino acids may be a cause of this change. Bacterial overgrowth in the bypassed segment and subsequent endotoxin related changes have been implicated.

### Microvesicular Steatosis

In direct contrast to macrovesicular steatosis, most causes of microvesicular steatosis present acutely. The common conditions are listed in Table 2. Acute fatty liver of pregnancy is a potentially fatal disorder, occurring in the third trimester between the 30th and 36th week of gestation. Patients present with nausea, vomiting, abdominal pain, jaundice and encephalopathy. It is commoner in twin pregnancies and with male foetuses. Probable
mitochondrial dysfunction, resulting in impaired oxidation of fatty acids, is the cause of this enigmatic condition. Roys's syndrome is another condition where microvesicular steatosis occurs as a result of preceding viral infection or salicylate ingestion. The other important causes are old tetracycline ingestion, fulminant hepatitis D and Jamaican vomiting sickness.

Prevalence

Fatty liver is a problem that has been reported worldwide. The true prevalence of fatty liver is difficult to assess in view of the varied study designs used. Table 3 summarizes the prevalence rates using different modalities of assessment.

<table>
<thead>
<tr>
<th>Study population</th>
<th>Prevalence (%)</th>
</tr>
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<tbody>
<tr>
<td>Patients undergoing liver biopsy</td>
<td></td>
</tr>
<tr>
<td>Propst et al</td>
<td>1.5</td>
</tr>
<tr>
<td>Hulcrantz et al</td>
<td>39</td>
</tr>
<tr>
<td>Patients undergoing CT scan</td>
<td></td>
</tr>
<tr>
<td>El-Hassan et al</td>
<td>9.7</td>
</tr>
<tr>
<td>Post-mortem of random deaths</td>
<td></td>
</tr>
<tr>
<td>Hildén et al</td>
<td>24</td>
</tr>
<tr>
<td>Ground et al</td>
<td>15.6</td>
</tr>
<tr>
<td>General population screening with ultrasound</td>
<td></td>
</tr>
<tr>
<td>Nomura et al</td>
<td>23</td>
</tr>
<tr>
<td>Lonardo</td>
<td>21.5</td>
</tr>
<tr>
<td>Bellantini</td>
<td>16.4</td>
</tr>
</tbody>
</table>

In patients undergoing liver biopsy the prevalence ranges between 1.5 and 39%. In the first study, biopsies were done on patients diagnosed to have fatty liver on ultrasonography, whereas in the latter study biopsies were done on all patients with elevated transaminases. This could account for the differences in these studies. They do not accurately reflect the true prevalence of fatty liver in the general population. The two reports studying random deaths in auto or plane accidents showed a prevalence of fatty liver in 24 and 16%, respectively. The corresponding prevalence rates for non-alcoholic steatohepatitis (NASH) was 2.4% and 2.1%, respectively. Prospective ultrasound based studies done in Japan and Italy have shown prevalence of fatty liver between 16.4% and 23%. However, these studies cannot correctly ascertain the exact pattern of histological involvement.

Clinical Characteristics

Patient Demographics

The majority of cases of non-alcoholic fatty liver occur in the fifth and sixth decades of life. Majority of the studies shows a definite female preponderance. The range is between 65-83%. The most common associated condition was type 2 diabetes mellitus that ranged between 28-55%. However, this is not the universal pattern. Fatty liver has also been documented in children and this is of concern. Non-obese male patients without diabetes and hyperlipidaemia have also been documented to have fatty liver in most series, though the proportion is less.
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Clinical and Laboratory Findings

Most patients (45-100%) with fatty liver are asymptomatic. The proportion who are symptomatic present with symptom complexes ranging from malaise & fatigue to right upper quadrant discomfort and pain. The commonest physical finding in patients with fatty liver is hepatomegaly which occurs in 12-75% of patients. When the diagnostic tool is ultrasonography hepatomegaly is detected in 95% of cases.

The most common biochemical abnormality is a minimal elevation of aminotransferases. However, 5-fold elevation of aminotransferases has also been documented. The common dilemma is to distinguish alcohol related injury from fatty liver. The AST/ALT ratio has been used to differentiate these two conditions and its usefulness has been validated. In patients with fatty liver the ratio is less than one in 65-90% cases. It has been postulated that if the ratio is more than one, the histological changes tend to be advanced.

Alkaline phosphatase and gamma GT are also mildly elevated. Serum albumin and serum bilirubin levels are mostly normal. Recent studies have postulated a role of iron in the pathogenesis of NASH. Elevated ferritin levels have been found in 50% of these patients. The identification of the HFE gene has added a new dimension to the pathogenesis of fatty liver. The postulate of iron overload worsening fatty liver was suggested in a study that showed that increased hepatic iron (Perls’ stain or HIC) had the greatest association with the severity of fibrosis. The Cys282Tyr mutation was responsible for most of the mild iron overload found in these patients leading to hepatic damage.

Clinical Significance

Microvesicular steatosis

The prognosis of all causes of microvesicular steatosis is bleak. Mitochondrial dysfunction is the postulated pathogenetic mechanism in microvesicular steatosis. This affects several cellular functions including urea synthesis, glucose metabolism and fatty acid oxidation. Biochemically, this results in hyperammonemia, hypoglycaemia and abnormalities of amino acid profiles. Morphological abnormality is not restricted to the mitochondria only. Abnormal ribosomes are also seen on electron microscopy. The maternal mortality in patients with AFLP is as high as 33% with a concomitant foetal mortality of 67%. Similarly, the mortality rate of Reye’s syndrome is around 30%.

Macovesicular Steatosis

This group is what is colloquially referred to as fatty liver. The natural history of this condition has traditionally been considered benign with no adverse clinical effects and no risk for progression to advanced stages of chronic liver disease. However these popular concepts have been proven wrong. When the underlying causative agent was alcohol, liver failure and even death has been reported with histopathology showing macrovesicular steatosis.

Secondly, several evidences point to the fact that fatty liver may not be just a static lesion but part of a continuum, which extends to fibrosis and then to cirrhosis. Patients with alcoholic fatty liver have biochemical evidence of increased collagen turnover. Animal models of alcoholic fatty liver have shown evidence of enhanced collagen deposition. The most compulsive evidence comes from long term follow up of such patients. Given below is a summary of such patients. The numbers sequentially biopsied are low and so the inference garnered may not be extrapolated to all. However, it makes for some compulsive observations.

The other major determinant relating to the progression of fatty liver is the pattern of histological involvement. A retrospective study looked at the progression to cirrhosis in four groups of patients. Group 1 had fat alone on histology. Group 2 had fat with inflammation. Group 3 had fat with ballooning degeneration and Group 4 had fat with fibrosis and Mallory’s hyaline. The last two groups had cirrhosis in 21% and 28% respectively which was significantly higher than the rate of 5% and 0% in the first two groups. This study suggested that inclusion of all types of histological patterns of fatty liver under one umbrella might be oversimplification of facts.
as various patterns tend to have variable prognosis. It also emphasized the need to standardize histological interpretation of fatty liver and NASH so that reliable natural history of this condition can be ascertained.

Various risk factors for progressive disease have been suggested. Angulo et al identified age, the AST/ALT ratio, and the presence of either obesity or diabetes as significant risk factors. These observations were corroborated by a similar study by Matteoni and colleagues. The reason for age being a risk factor may be only a reflection of the duration of time that the patient has had steatosis, leading on to subsequent injury. It is worth noting that this pattern may change in the Western population, with obesity and hepatic steatosis being increasingly recognized in children. The AST/ALT ratio has been used to document fibrosis in viral hepatitis C and can be used in the same vein in fatty liver.

There are other studies, which have shown that fatty liver may be a cause of cryptogenic cirrhosis. It has been postulated that with time the degree of steatosis slowly regresses and may be absent in the terminal phase of cirrhosis.

**Conclusion**

Fatty liver is a common clinical condition where there is excessive accumulation of fat within the hepatocytes. Two main patterns of histology are seen: microvesicular and macrovesicular. Microvesicular steatosis presents acutely, is associated with mitochondrial dysfunction and has a uniformly grave prognosis. Macrovesicular steatosis is associated with chronic diseases. It is one end of a spectrum of illness, which progresses to NASH and cirrhosis. Histological pattern of injury, age, concomitant diabetes or obesity and AST/ALT ratio predict progression of disease. It is postulated that fatty liver may be a cause for cryptogenic cirrhosis. All this seems to suggest that fatty liver is not as benign as considered previously.

**Table 4: Fatty liver with sequential biopsies**

<table>
<thead>
<tr>
<th></th>
<th>Histology</th>
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<tbody>
<tr>
<td></td>
<td>n/Total* Improved No change Fibrosis Cirrhosis</td>
</tr>
<tr>
<td>Lee</td>
<td>12/38 0/12 7/12 3/12 2/12</td>
</tr>
<tr>
<td>Powell</td>
<td>12/41 1/12 5/12 4/12 2/12</td>
</tr>
<tr>
<td>Bacon</td>
<td>2/33 0/2 0/2 0/2 1/2</td>
</tr>
<tr>
<td>Cumulative</td>
<td>4% 50% 27% 19%</td>
</tr>
</tbody>
</table>

* Represents the number of patients out of the total group who had biopsies.

**References**
