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## Non-Alcoholic Fatty Liver Disease: A New Urban Epidemic

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### ABSTRACT

*Non-alcoholic fatty liver disease (NAFLD) comprises of a spectrum of pathological changes in the liver. It has become a very common disease in the urban population. Understanding the pathophysiological mechanisms underlying this disease is pivotal in planning a management strategy. The etiopathogenesis, clinical features, diagnosis and management is discussed in this paper.*

**Keywords:** non-alcoholic, fatty, liver, disease, steatohepatitis,

### INTRODUCTION

The traditionally used term fatty liver was synonymous with early alcoholic liver disease. However extensive research over period of time has revealed that a variety of other causes can lead to liver changes exactly simulating alcoholic liver disease. This has led to a confusion in the

nomenclature. The non-alcoholic variant is now classically described as non-alcoholic fatty liver disease. Non-alcoholic fatty liver disease (NAFLD) is typically described as a condition characterized by lipid deposition in hepatocytes of liver parenchyma. The condition has assumed epidemic proportions in urban population.

## DEFINITION

The condition was initially described as NASH i.e. Non Alcoholic Steatohepatitis. [1] The histologic features closely simulate alcoholic liver disease. However when it was understood that there is a wide spectrum of conditions having similar histological findings but with varying severity, the condition was named as NAFLD. [2]The spectrum of histological finding ranges from simple fatty liver typically described as hepatic steatosis to non-alcoholic steatohepatitis (NASH) which is characterized by significant fatty changes, lobular inflammation, and presence of Mallory hyaline with progressive fibrosis eventually leading to cirrhosis.[2,3]

## ETIOPATHOGENESIS

Though the worldwide prevalence is yet to be determined it is approximately present in 10-24 % urban population. [4] With improved nutrition obesity has become rampant across all age groups. Obesity is associated with insulin resistance and dyslipidaemia. This triad constitutes a very important precursor to the development of NAFLD. [4]

Though the exact pathogenesis of NAFLD is still a challenging topic for research, various hypothesis have been put forward. The hit theory is the most commonly accepted one. [5] Hit refers to the insult inflicted onto the hepatocytes. Multiple hits lead to progressive liver injury. The initial hit is by virtue of insulin resistance which most likely plays a central role in net retention of lipids within the hepatocytes. This is most

probably the result of decreased disposal of fatty acids due to impaired mitochondrial beta oxidation. The second hit or insult is generally attributed to oxidative stress which causes lipid peroxidation in the hepatocyte membrane in addition to cytokine production and Fas ligand induction. This is supposed to be responsible for progression of mild disease or steatosis to NASH eventually leading to cirrhosis. Obesity is associated with alteration of leptins. Increase serum leptins promotes the development of NAFLD. [6, 7] The role of iron by virtue of stellate cell activation and collagen deposition is still undergoing investigation. [8,9]

The molecular basis of obesity related NAFLD has been studied on the rat model which has phenotype features similar to human obesity.[9] These rats exhibit insulin resistance and dyslipidaemia as well. The rats exhibited oxidative stress, endoplasmic reticulum stress, mitochondrial dysfunction and decreased expression of survival genes. [7] Extra hepatic signals may add to the complexity of injury. These are by virtue of peripheral insulin resistance associated with an increase in adipose mass and systemic free fatty acids. NAFLD is seen in patients suffering from hepatitis C and inflammatory bowel disease. [10,11] NAFLD happens to be a result of inflammatory bowel disease, seen in 10-20% of IBD patients.[11] NAFLD has also been sighted as a predisposing factor for colorectal neoplasms.[12] The higher prevalence of colorectal neoplasms especially right sided colon have been noted.[12] Therefore

colorectal cancer screening is strongly advisable in this high risk group. The natural history of NAFLD is variable depending upon the severity of liver injury. [13] 25% of patients may progress to cirrhosis and portal hypertension. The relationship between comorbidities of coronary disease and malignancy add to complexity of the natural history. NAFLD has been found to be a risk factor for a variety of extra hepatic diseases such as chronic vascular disease, chronic kidney disease, colorectal cancer as described, thyroid disorders and osteoporosis. [14]

### DIAGNOSIS

Majority of patients of NAFLD are asymptomatic in whom the condition may be diagnosed during a routine annual health check. The symptomatic group in the early stages may present with mild fatigue, increase flatulence and mild upper abdomen discomfort. [2] Nausea, anorexia and malaise may be present. Asymptomatic disease if left undiagnosed and untreated may present with lethal complication of cirrhosis at a later date. [3, 4]

Physical examination of patient with NAFLD usually exhibit high or low BMI and hepatomegaly. [3,4] High BMI is seen in obese diabetic patients with altered lipid profile where as low BMI may be associated with surgical procedures on the gut, rapid weight loss, starvation, protein energy malnutrition as seen in vegans. History of inborn errors of metabolism and drug therapy may also be associated with NAFLD. [2,3,4] Anticancer drugs such as

methotrexate, nucleoside analogues and tamoxifen are associated with NAFLD. [2,3,15, 16] In a few cases patients present with signs of hepatocellular failure due to cirrhosis. [8]

### INVESTIGATIONS

Mild to moderate elevation of serum aminotransferases is the commonest abnormality. In NAFLD the AST: ALT ratio is usually <1 ratio but tends to increase with development of cirrhosis thereby losing its accuracy. Alkaline phosphatase may be elevated in few patients. Elevated lipid profiles and blood glucose concentrations are seen in 25-75% of patients. A minority of patients with NAFLD may have low titre of positive antinuclear antibodies (ANA). Few patients may also exhibit elevated serum iron suggestive of overload. Hepatitis C (HCV) may be a concomitant finding in a select few cases of NAFLD.

### RADIOLOGICAL INVESTIGATION

Ultrasound (USG), CT scan and MRI have been advocated as diagnostic tests for NAFLD. USG however is the most important screening as well as diagnostic test. The findings on USG include diffuse hyper-echoic texture of the liver, vascular blurring and deep attenuation. [15] The hepatic echo texture is usually denser than that of the kidney. CT scan may show typically a low density liver parenchyma. Magnetic resonance spectroscopy is a new method proposed to diagnose NAFLD. However its diagnostic role requires confirmation.

**Liver biopsy** is the most accurate method for diagnosing NAFLD. [3, 4, 15, 16] However the investigation needs to be used judiciously in view of a variety of morbid complications. Typically histological features are predominantly

- macro vascular steatosis alone
- macro vascular steatosis and varying amount of cytological ballooning, spotty necrosis, scattered inflammatory foci, glycogen nuclei, peri-sinusoidal fibrosis.

The severity of steatosis may be graded on the basis of the extent of the involvement of the liver parenchyma. [16]

## TREATMENT

Weight management and medications are mainstay of treatment.

An appropriate diet and exercise program leading to 10 % gradual weight loss can lead to improvement in liver biochemistry and histology. [15] This can also provide benefits to patients with cardiovascular disorders. However rapid weight loss can have disastrous consequences as it can cause worsening of steatohepatitis and can precipitate liver cell failure. Bariatric surgery has also been proposed. However the risk of developing decompensated liver disease during rapid weight loss post operatively remains high. [15, 16]

Medical treatment aims at controlling insulin resistance. [16] Thiazolidinediones are drugs of choice as they improve insulin sensitivity. This drug administered for 3-6 months showed normalization of ALT. However the long

term safety of these drugs precludes their routine use in NAFLD.

Metformin another OHA which improves insulin sensitivity is also associated with decreased aminotransferase activity. [16]

As these observation are based on studies with very small sample size, more rigorous studies with a large sample size are required to substantiate and standardize the therapeutic protocol of these drugs.

Lipid lowering agents have also been tried. Clofibrate was the first medication to be tried but unfortunately did not yield positive results.

Gemfibrosil is another drug which showed significant improvement in ALT levels. However due to paucity of medical data these drugs cannot be routinely advised as a standard of practice.

The most commonly used pharmacological therapy is that which offers hepatocyte protection. These agents include Ursodeoxycholic acid (UDCA) and antioxidants like betaine and Vitamin E. [15, 16] The therapeutic role of UDCA was extensively studied. However the results did not reveal any improvement in liver biochemistry and histology.

Vitamin E (alpha tocoferol) in the dose of 400-1200 IU daily was associated with significant improvement in liver enzymes. However significant improvement was also seen in fibrosis scores in NASH. [16]

A combination of Pioglitazone and Vitamin E was found to deliver more therapeutic benefits as compared with Vitamin E alone.

Betaine, a normal component of metabolism of methionine is a precursor of S-adenosine methionine (SAM) which is supposed to have hepatoprotective effect. However the results need to be confirmed with long-term prospective trials. Liver transplantation has been offered to patients with NAFLD presenting as endstage liver disease. However the results are dismal with development of NAFLD in the transplanted liver. [16]

Other agents such as tricholine citrate, sorbitol and ornithine containing compounds also exert a protective effect thereby leading to resolution of biochemical and radiological changes in NAFLD. However data on the effect of these medications on histology is lacking.

## CONCLUSION

NAFLD is a complex liver disease with a wide spectrum of changes in the liver parenchyma.

No specific therapeutic medical regimen can be advised authentically for cure of the disease.

Treating the underlying metabolic derangements is therefore the mainstay of treatment.

Gradual supervised weight reduction and improvement in insulin sensitivity accompanied with hepatoprotective agents remain the mainstay of treatment.

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