Short Communication

Fatty Liver- No Longer Benign !

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Fatty Liver - Changing Concepts

♦ **NAFLD (Nonalcoholic Fatty Liver Disease) :**

- NAFLD is the most common cause of chronic liver disease in Western nations
- 4^{th} – 6^{th} decades of life
- Men > Women
- Hepatic manifestation of metabolic syndrome
- Evidence of excessive fat accumulation in the form of triglycerides (steatosis) in the liver by histology (> 5% of hepatocytes) or imaging (> 33% of hepatocytes)
- There should be no causes for secondary hepatic fat accumulation

Table 2. Common Causes of Secondary Hepatic Steatosis

Macrovesicular steatosis

- Excessive alcohol consumption
- Hepatitis C (genotype 3)
- Wilson's disease
- Lipodystrophy
- Starvation
- Parenteral nutrition
- Abetalipoproteinemia
- Medications (e.g., amiodarone, methotrexate, tamoxifen, corticosteroids)

Microvesicular steatosis

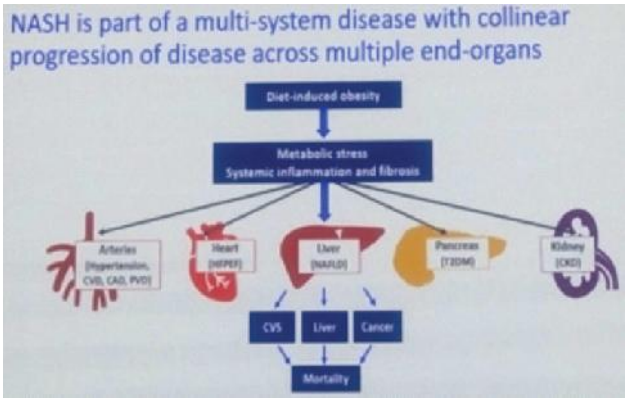
- Reye's syndrome
- Medications (valproate, anti-retroviral medicines)
- Acute fatty liver of pregnancy
- HELLP syndrome
- Inborn errors of metabolism (e.g., LCAT deficiency, cholesterol ester storage disease, Wolman disease)

Prevalence of NAFLD		
India	Asia	West (USG + Biopsy)
Ultrasound		NAFLD 46%
9-30 %	15-30%	NASH 12.2%

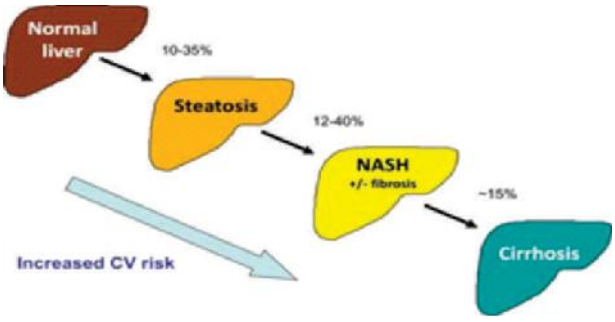
	NAFLD	NASH
Patients with **bariatric surgery**	91%	37%
Diabetes	60-76%	22%

NASH (Non-alcoholic steatohepatitis)

- >80% of NAFLD pts have an increased BMI
- 30-40% are obese
- ~50% show signs of insulin resistance
- 20-30% have type 2 diabetes
- 80% show hyperlipidemia



• Natural history of NAFLD •



- **Most common cause of death in patients with NAFLD is cardiovascular disease.**
- **HCC (Hepatocellular carcinoma) and liver related events in NAFLD largely occur in advanced fibrosis and cirrhosis.**
- **When to suspect NAFLD?**

A. Presence of risk factors:

– Overweight-obesity

– Features of metabolic syndrome- T2DM

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B. Liver injury without other causes:

– Abnormal AST, ALT

C. Direct evidence of increased hepatic fat:

– Imaging (US, CT scan, MRI)

SYMPTOMS	SIGNS
1. None (48 - 100%)	**1. Hepatomegaly (75%)**
2. Vague RUQ pain	2. Splenomegaly
3. Fatigue	3. Spider angiomata
4. Malaise	4. Palmar erythema

♦ **Laboratory Investigations:**

- **2 to 4 time ↑ of serum ALT and AST levels (Invariably below 250 IU/l)**
- **AST/ALT ratio < 1**
- S. alkaline phosphatase slightly elevated (1/3)
- S.bilirubin, S.albumin and PT usually Normal
- Elevated serum ferritin level (20-50%)

♦ **Imaging :**[2]

A. Hepatic Ultrasound: Fatty liver

B. Hepatic CT Scan

– Steatosis decreases CT attenuation of the liver (10 or more Hounsfield units lower than spleen on a noncontrast-CT)

C. MRS (Magnetic resonance spectroscopy) is the best modality.

D. None of these methods can diagnose steatohepatitis or accurately assess the stage.

♦ **Is Intervention needed?**

Table 85-A – Risk Factors for Advanced* Nonalcoholic Fatty Liver Disease

Clinical
Older age (>50 years) Obesity Diabetes mellitus/insulin resistance Hypertension
Laboratory
AST/ALT ratio > 1 Serum ALT level > twice the upper limit of normal Serum triglyceride levels > 155 mg/dL
Histologic
Severe steatosis Necroinflammatory activity (hepatocyte ballooning, necrosis) Stainable iron

♦ **Noninvasive Markers of Fibrosis in NAFLD**

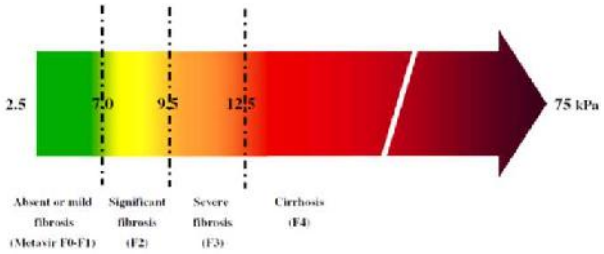
A. Fibrosis (FIB) – 4 score3

FIB-4 = **(Age x AST) / (Platelets x √(ALT))**

- Fib-4 score < 1.30 = F0-F1
- Fib-4 score > 2.67 = F3-F4
- Liver biopsy could have been avoided with **86%** accuracy.

B. Transient elastography (Fibroscan)[4]

- Uses ultrasound waves to **quantify liver stiffness** and **estimate fibrosis**
- Works well in determining extremes of liver disease - minimal scarring from cirrhosis.
- **Liver stiffness: 2.5 to 75 kPa (kilo-pascals)**
- **Cut off for cirrhosis is 12.5 kPa**
- Results operator-independent



♦ **NAFLD & Liver Biopsy**[5]

- Histology – **only proven method to distinguish NASH from steatosis**
- Gold standard for **fibrosis grade and stage**
- **Advantages:**

– Allows **diagnosis** & provides **prognosis**

– Selection for **surveillance for Cirrhosis & HCC**

- **Limitations:**

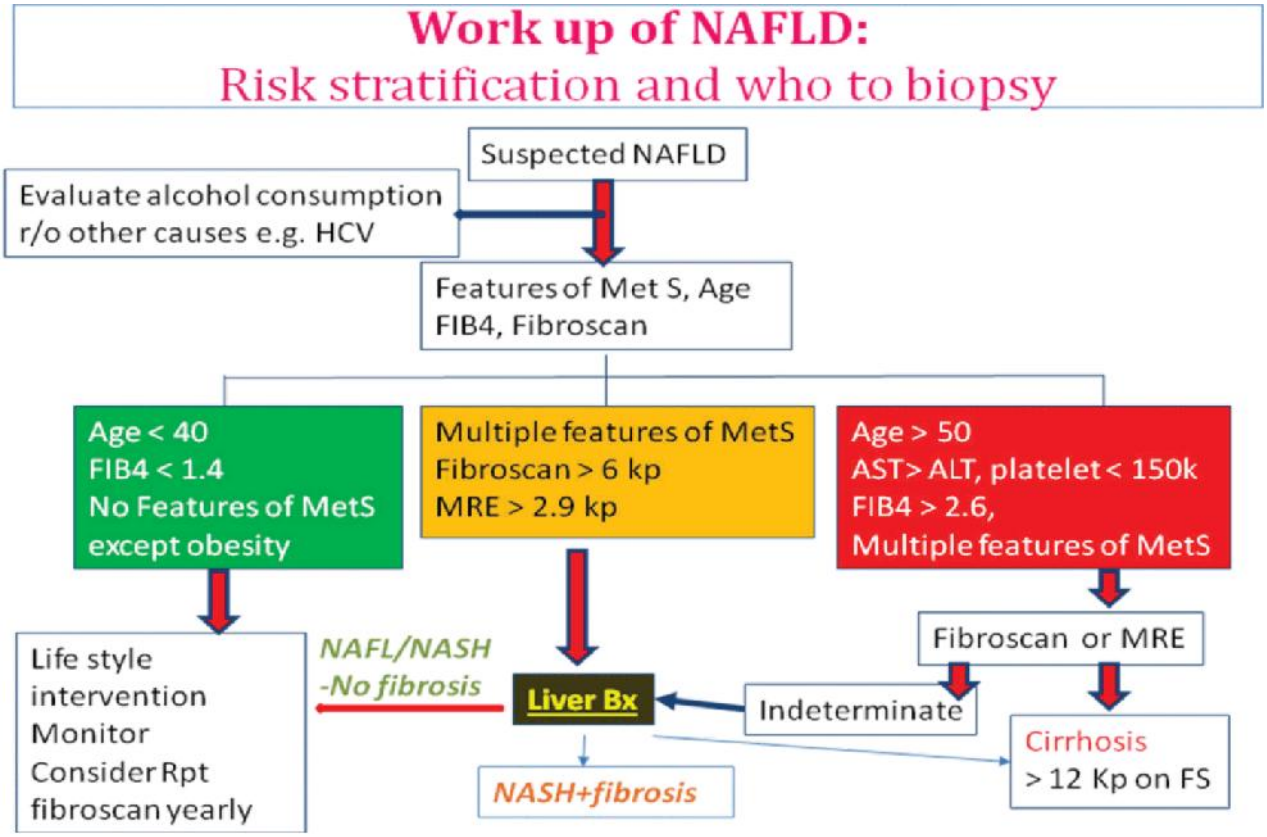
– Potential for clinical risk and **potential false negatives**

– **Variation in interpretation**

- **RECOMMENDATION for Liver Biopsy**
  - NAFLD who are at **increased risk to have steatohepatitis and advanced fibrosis.**
  - Suspected NAFLD in whom **etiologies** for hepatic steatosis and co-existing **CLD** cannot be excluded without a liver biopsy

♦ **Goals of therapy**[6]

- Improve all cause mortality, quality of life and functional outcomes:
  - **Cardiovascular outcomes**
  - **Liver related outcomes**
  - Cancer related outcomes



♦ **Dietary Modification**[7]

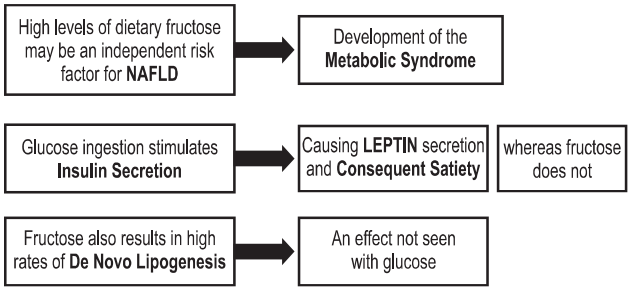
♣ **Total calorie restriction:** ((1,200-1,500 cal/d)

- Most important goal for steatosis → Leads to weight loss

♣ **Macronutrient modification:**

- Low carbohydrate diet vs. Low Fat diet
  - Both similar to lower liver fat, serum ALT and induce weight loss.
- Low carbohydrate diet (50% whole grain)
  - Better in improving insulin sensitivity in pts. with glucose intolerance
- Low fat diet (35% total energy): Less saturated fat, More Polyunsaturated Fat

♦ **Dietary Modification- Fructose avoided**



✓ High Dietary FRUCTOSE should be avoided

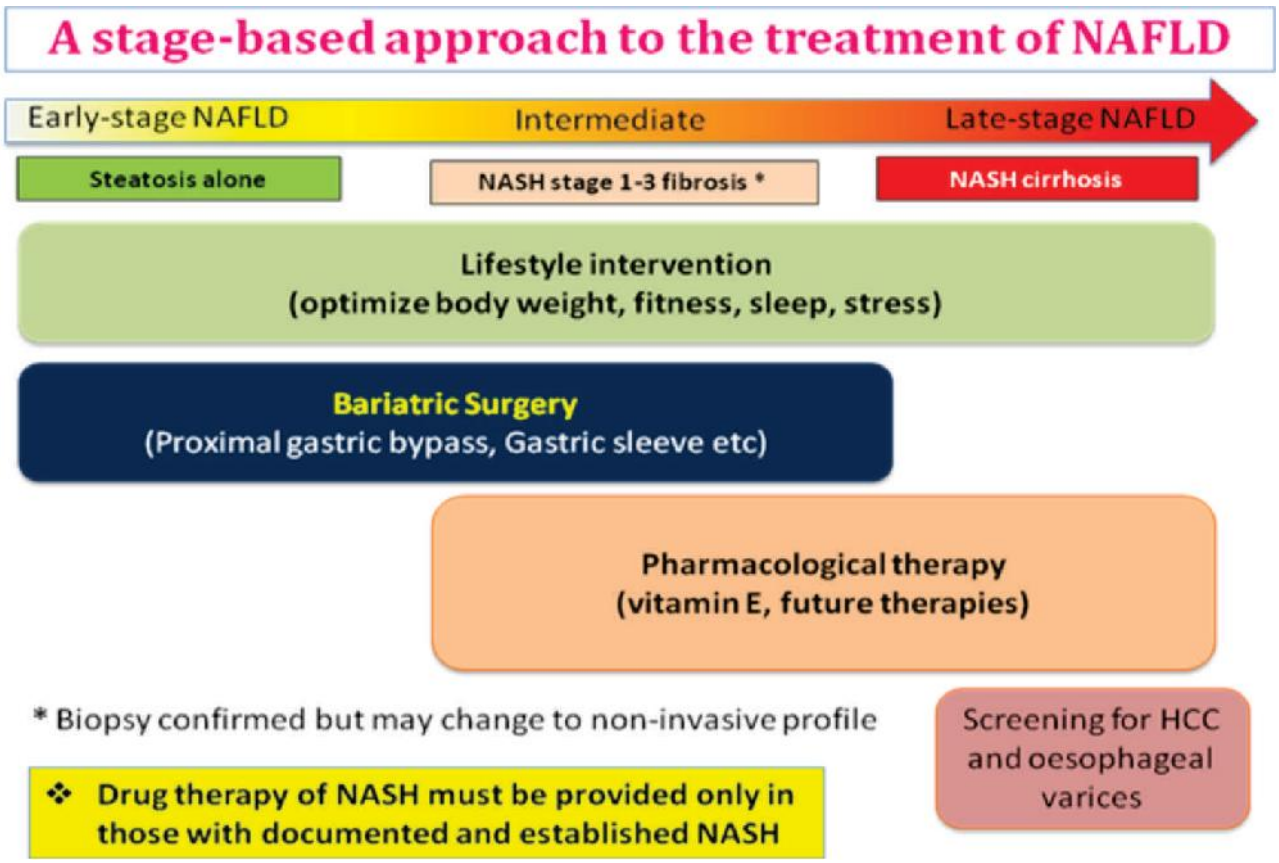
✓ Modest amounts of naturally occurring sources such as fruit are permissible.

♦ **Weight loss intensity is strongly associated to improvement of histological parameters in patients with NASH after 52 weeks of lifestyle modification8**

- **5% weight loss improves steatosis**
- **7% weight loss improves steatohepatitis**
- **10% weight loss improves fibrosis in 45% of patients at 1 year**

♦ **Vitamin-E:**[9]

- Vitamin E 800 IU/day improves liver histology in **biopsy-proven NASH**
- **Should be considered as a first-line therapy**
- **Vitamin E is not recommended to treat**
  - √ NASH in diabetic patients
  - √ NAFLD without liver biopsy
  - √ NASH cirrhosis/Cryptogenic cirrhosis



♦ **Other Therapies (Not proven benefits)**

- Ursodeoxycholic acid (UDCA)
- S-Adenosyl Methionine
- N-acetylcysteine
- Statins
- Metformin
- Omega-3 Fatty acids

♦ **Liver Transplantation**

- NAFLD with ESLD should be evaluated for liver transplantation
- Outcome in these pts is good, although NAFLD can recur after transplantation

♦ **Future Drug therapies for NAFLD**

1) Elafibranor

– PPAR a/d agonist – Peroxisome proliferator activated receptor

2) Saroglitazar

– Dual PPAR a and g agonist

3) Obeticholic acid

– Semi-synthetic bile acid

4) Licogliflozin

– SGLT 1/2 Inhibitor (Sodium dependent Glucose cotransporters)

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