Non-alcoholic Fatty Liver Disease (NAFLD)
(Fatty Liver)

Smruti R. Mohanty, MD, MS
Assistant Professor of Medicine
Center for Liver Diseases
Section of Gastroenterology
University of Chicago
September 29, 2006

Learning Objectives
- Define Fatty liver
- History of Fatty Liver
- Rate of Fatty liver
- Demographic Features and racial variations in fatty liver
- Risk Factors for fatty liver
- Relationship between metabolic syndrome and Fatty Liver
- Development of Fatty Liver
- Clinical Presentation & Diagnosis of Fatty Liver
- Role of Liver Biopsy in Fatty Liver
- Natural History of Fatty Liver
- Treatment of Fatty Liver

What is Fatty Liver (Non-Alcoholic Fatty Liver)?
- Simple term called "Fatty Liver"
- This is a spectrum of disorder characterized by accumulation of fat within the liver cells, with or without inflammation of liver or liver cell injury or damage.
- Patients lack the significant history of alcohol drinking.

Diehl et al., Gastroenterology 1988; 95: 1056-1062

Fatty Liver (NAFLD)
- Fatty Liver (NAFLD) can be progressive
  - Fat accumulation in liver (Steatosis)
  - Fat + Inflammation and liver cell injury or damage
    ---- Non-alcoholic steatohepatitis (NASH)
  - Non-alcoholic steatohepatitis + Fibrosis (scar tissue in the liver)
  - Cirrhosis (multiple nodules formation from scar tissue)
  - Liver Cancer (Cancer from Liver Cells)

Diehl et al., Gastroenterology 1988; 95: 1056-1062
What is the History of Fatty Liver (NAFLD/NASH)?

- Fatty Liver has been known for two decades
- Non-alcoholic steatohepatitis (fat + inflammation + scar tissue)
  - a subset or spectrum of Fatty liver
- 1980-First reported by Ludwig et al. at Mayo
  - In liver biopsy, features of alcoholic Hepatitis suggestive of fatty Liver (identical to alcohol related liver damage due to drinking)
  - Patients lack a significant history of alcohol drinking
  

What is the Rate/risk of Fatty liver in general population?

- True rate of fatty liver in general population is lacking.
- It may be more common disease in general population.
- Most diagnosis are made by imaging or liver tests
  - Inability to distinguish between simple fatty liver vs. fat with inflammation or damage (NASH) or Cirrhosis
- Studies with liver biopsies looked at specific groups such as obesity or diabetes
  - Selection bias or referral bias


What is the Rate/risk of Fatty liver in general population? (Cont.)

- population based studies (radiology survey, postmortem studies)
- 16% - 23% of general population
  - NASH (fat with damage to liver) in 2% - 6% cases
- Fatty liver in Children
  - 2.6% of pediatric population
  - 22.5% - 52.5% of children with obesity
  - Some children have cirrhosis

  Clark JM et al. Gastro 2002; 122:1649-1657

Demographic Features

- Increased rate of obesity over last three decades
  - Entire spectrum of fatty liver in all age groups
- Highest rates in 4th or 5th decades (40 or 50 years) of life
- Fatty Liver affects both sexes equally
- True rate among various racial and ethnic groups is not fully known
  - Mexican Americans > Caucasians > African Americans
  - Lower prevalence of NAFLD among African Americans, may be related to referral patterns, genetic differences and lack of disease recognition.
Demographic Features (Cont.)

- Familial Clustering (Several members of family)
  - Person's genetic factors may play a major role, but data is not available
  - Studies on Multiple Family members with fatty liver
    - No clear inheritance patterns
  - Diabetes and Obesity (risk factors for fatty liver) showed familial clustering
    - Rare familial disorders or diseases
      - Abetalipoproteinemia and lipodystrophies lead to fatty liver and cirrhosis
      - Different patterns of genes may play role in the development of fatty liver in these disorders

Racial and Ethnic Variations in fatty liver

Ruhl et al. Gastroenterology 2003;124:71-79

What are the major risk factors?

Metabolic syndrome
  (Diabetes, Over weight, High Blood pressure, high cholesterol)
  - Diabetes
  - Obesity

Other Risk Factors for fatty liver

- Alcohol
- TPN (nutrition through vein)
- Wilson diseases
- Jejunileal bypass
- Starvation
- Lipodystrophy
- Abetalipoproteinemia
- Weber-Christian Syndrome
- Industrial Toxins
- Hypothyroidism (low thyroid function)
- Medications
  - Corticosteroids
  - Amiodarone
  - Tamoxiphen
  - Diltiazem
  - Nifedipine
  - Methotrexate
  - HAART (HIV drugs)
Metabolic Syndrome and Fatty Liver

- Fatty liver is associated with Metabolic syndrome (insulin resistance)
  - Obese, diabetes and high triglyceride (fat in the blood)
- 60%-95% of patients with Fatty Liver are obese
  - In Morbid obese, the rate of fatty liver is ≥ 95%
  & rate of fatty with damage/scar tissue (NASH) is approximately 25 %
- 21%-55% of patients with fatty liver have Diabetes
  - Diabetes is associated with advanced scar tissue and cirrhosis
- 21%-55% of patients with fatty liver have high triglyceride (fat in the blood)

Mokdad et al. JAMA 2001

Relationship between insulin resistance and Fatty Liver

- DM and Obesity leads insulin Resistance (IR)

Insulin Resistance ➔ Fat in Liver

Questions

How do we make diagnosis of NAFLD / NASH ?

Which patients need Liver Biopsy ?

How do we manage these cases ?

Is NAFLD / NASH lead to cirrhosis ?

Clinical Presentation of NAFLD

- Symptoms
  - Asymptomatic
  - Non-specific symptoms
  - Symptoms related to Metabolic syndrome
  - Fatigue is very common
  - Symptoms of Sleep apnea related to obesity
  - Occasionally, RUQ pain
    - Common in children

- Signs
  - Obesity is most common
  - High blood pressure
  - Hepatomegaly (50%)
  - Signs related chronic liver diseases
  - Muscle wasting
  - Pruritus, anorexia and Jaundice (advanced liver dysfunction)
  - Signs of portal hypertension
Laboratory Abnormalities

- Elevated liver tests when checked for nonspecific symptoms
- 30% - 50% have Diabetes or Glucose intolerance
- 20% - 80% have High cholesterol

What is the role of Imaging studies in Fatty Liver?

- U/S, CT and MRI Fatty infiltration in liver
  - Can not differentiate simple fat vs fat with scar tissue
  - Unable to recognize hepatic scar
  - Morbid obese individuals ultrasound image may be poor and unable to recognize liver fat

Is there a role of Liver Biopsy in Fatty liver?

- Liver biopsy is gold standard for the diagnosis
- It can differentiate simple fat vs fat with inflammation and scar tissue
- Stages of scar and/or Cirrhosis
- 20% patients with increased liver tests may have alternate diagnosis on liver biopsy
- Liver biopsy should be individualized
How do we make a diagnosis of Fatty Liver?

- The patient have no significant alcohol intake
  - No more than 1-2 drinks per day
- Other liver diseases be ruled out
  - HCV, Wilson’s disease and drugs etc.
  - Fatty liver may co-exist with other liver diseases
- The liver biopsy feature compatible with fatty liver
What is Natural History of Fatty Liver?

- Can fatty liver be progressive?
- What is the prognosis?
- Does fatty liver disease lead to liver cancer?

Can Fatty Liver be progressive?

- Generally, patients with simple fat in liver have non-progressive fatty liver
- But one study has shown that simple fat liver may progress to progressive liver disease
- Fatty liver may progress to cirrhosis and can have liver related death


Does Fatty Liver disease lead to liver cancer?

Data also suggest that fatty liver may be an important cause of cirrhosis and liver cancer.

Natural History of Fatty Liver (NAFLD)

- Normal Liver
- Simple Fat
- Fat + Inflammation 20%
- Fatty Liver + Scar tissue
- Cirrhosis
- Liver Cancer
Treatment of Fatty Liver

• Currently, there is no proven effective therapy.
• Focus on modifying associated conditions
  – Metabolic Syndrome
  – Diabetes
  – Obesity
  – High Cholesterol

Treatment of Fatty Liver (Cont.)

• Weight loss
  – Wt. loss > 10 % leads improvement of liver enzymes and improvement of fat
  – Rapid Wt. loss may lead to increased inflammation and scar tissue in liver including liver failure
  – Gradual wt. loss of 10 % of baseline wt is recommended
  – No significant data on liver scar tissue improvement those who lost weight
• Management of high cholesterol
  – Cholesterol lowering agents may be associated improvement of liver cell injury, inflammation and liver tests

Treatment of Fatty Liver (Cont.)

• Increase insulin sensitivity
  – Metformin
    • Pilot study (14 patients) showed improvement of LFTs
  – Thiazolidinediones
    • Rosiglitazone & Pioglitazone (diabetic drugs)
    • Liver test and liver inflammation/scar tissue improvement
    • Potential liver toxicity
    • Those drugs are not FDA approved for fatty liver yet.

Neuschwander-Tetri et al., Hepatology 2003
Promrat K et al., Hepatology 2004

Treatment of Fatty Liver (Cont.)

• Vitamin E
  – Small pilot studies showed improvement of liver tests and liver inflammation/scar tissue in obese children and patients with fatty liver

Summary

• Growing incidence of obesity in general population has made fatty liver disease and its complications the major public health issue.
• Fatty liver disease is associated with non-specific symptoms.
• Asymptomatic presentation does not imply benign course.
• Fatty Liver can be progressive and may lead to cirrhosis and liver cancer.

Summary (Cont.)

• Currently, there is no proven effective treatment or therapy.
• Mainstay of treatment is therapy for associated conditions such as metabolic syndrome, control of diabetes, high cholesterol and weight loss.

Thank you