NONALCOHOLIC STEATOHEPATITIS

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Definition of NASH

Nonalcoholic steatohepatitis (NASH) is the term used to describe the distinct clinical entity in which patients lack a history of significant alcohol consumption but have liver biopsy findings indistinguishable from alcoholic hepatitis.

Criteria for Dx of NASH

- Liver bx shows macrovesicular fatty change with inflammation and with or without Mallory bodies, fibrosis or cirrhosis.
- Convincing evidence of negligible alcohol consumption (less than 10 g/day of alcohol for women and less than 20 g/day for men).

Ultrasound showing

Bright echogenic liver

Liver Ultrasound Report

The liver is enlarged. It is diffusely echogenic consistent with fat infiltration of the liver. Other forms of liver disease and more advanced liver disease including early cirrhosis cannot be excluded by this study.
Biopsies

macrovesicular steatosis (zone III)

NASH: Liver Histology

lobular sinusoidal neutrophils

Ballooning degeneration

Sinusoidal pericellular fibrosis, trichrome stain

NASH is Likely a Major Cause of Cryptogenic Cirrhosis

• 74% of 70 consecutive patients with cryptogenic cirrhosis had obesity and/or diabetes

• This percentage is similar to prevalence of obesity and/or diabetes noted in 50 consecutive patients with NASH
Epidemiology of NAFLD

- Estimate: 40 million Americans have NAFLD
  5 million are cirrhotic

- Majority of pts with NASH have metabolic syndrome

- Over age 60 years, 40% have metabolic syndrome

NAFLD is Part of the Metabolic Syndrome
Called Syndrome X

- Obesity
- Hypertriglyceridemia
- Hyperinsulinemia
- Hypertension
- Insulin Resistance
- Diabetes

Patients with NASH

<table>
<thead>
<tr>
<th>Normal ALT</th>
<th>Increased ALT</th>
<th>p.value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrosis Stage 2 or greater</td>
<td>22%</td>
<td>34%</td>
</tr>
</tbody>
</table>


Other Conditions Associated with NASH

- Drugs or Toxins
- Abdominal Surgery
- Metabolic Disorders
- Miscellaneous

K-F Ring

One disorder that is critical to exclude in young individuals is Wilson’s disease
Drugs Associated with NASH

- Glucocorticoids
- Tamoxifen
- Synthetic estrogens
- Perhexilene maleate
- Amiodarone
- Isoniazid

Progression to Cirrhosis

<table>
<thead>
<tr>
<th></th>
<th>10 Yr Survival</th>
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<tbody>
<tr>
<td>Alcoholic</td>
<td>38 - 50%</td>
</tr>
<tr>
<td>Hepatitis</td>
<td></td>
</tr>
<tr>
<td>NASH</td>
<td>8 – 26%</td>
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</table>

Clinical Features of NASH

Symptoms

- Asymptomatic
- Fatigue
- RUQ Discomfort or Pain

Laboratory Features of NASH

- ALT and AST 2 to 4 fold elevated in most patients
- Alk phos mildly elevated in a third of patients
- Albumin, PT, bilirubin most often normal
- Serum ferritin elevated in half the patients

Patients with Suspected NASH should Undergo Liver Biopsy

Pros

- NASH is a histologic dx
- Poor correlation between lab findings and histologic severity
- Biopsy results may change management

Cons

- Small but finite risk of complications
- Biopsy results may not change management
- Limited manpower

Suspected NASH: Reasonable to perform liver biopsy

If any of following present

- Peripheral stigmata of chronic liver disease
- Splenomegaly
- Cytopenia
- Abnormal iron studies
- Diabetes and/or significant obesity in a patient over 45 years of age with elevated ALT
Are there alternatives to liver biopsy?

Fibrotest (fibrosure)

Alpha 2 macroglobulin, haptoglobin, gamma globulin, GGT, total bilirubin, apolipoprotein A1

The severity of disease was correctly identified in 46% of patients.

Am J Gastroenterol 2006

Fibroseure. I am not so sure!

Fibroscan

- Non-fasting
- Examination time < 5 minutes
- Median value of 10 successful acquisitions
- Sampling error
  - Biopsy – 1/50,000
  - Fibroscan – 1/500

Sampling

- Liver biopsy samples only 1/50,000th of whole liver.
- Fibroscan samples 1/500th of whole liver.

Hepatic Elastography

- Fibroscan is a rapid and non-invasive measure of hepatic stiffness
- Hepatic stiffness correlates with fibrosis
Likely Future Scenario
Patients with suspected Liver Disease

Biomarkers and Fibroscan

- Low likelihood of fibrosis
  - No liver biopsy
  - Follow or treat

- Grey zone
  - Liver biopsy

- High likelihood of fibrosis
  - No liver biopsy
  - Screen HCC, varices

Progression of NAFLD
Initial Biopsy Results May Be Useful
- Fat Alone: Progression to Cirrhosis - 5%
- Ballooning Degeneration and Mallory Hyaline or Fibrosis: Progression to Cirrhosis - 25%

Pathogenesis of NASH
- Perturbation of fatty acid processing.
- Insulin resistance
- Lipid peroxidation and oxidative stress*
  * Potential oxidative stressors include: hepatic iron, intestinal bacteria, leptin and states characterized by anti-oxidant deficiencies

Prevention and Treatment of NASH
- Prevention of obesity and metabolic syndrome
- Treatment of metabolic syndrome
- Coffee?
- Bariatric Surgery if appropriate
Pioglitazone therapy over a 12 month period in nondiabetic NASH patients resulted in improvement in biochemical, metabolic and histological parameters (including fibrosis).

Aithal GP, et al. Gastroenterology 2008: 135;1176

NASH: Weight Loss is Beneficial!

1. 9% or greater weight loss resulted in:
   • Biochemical improvement
   • Histologic improvement (steatosis, ballooning, inflann*)
   • Improvement in Insulin resistance
   • Higher Adiponectin levels

2. Following bariatric surgery, Hepatic Fibrosis improved or was reversed in 66%.

Vitamin E May Have Benefit

• 247 Adults with NASH (without diabetes) randomly assigned to pioglitazone (30 mg. daily) Vitamin E (800 IU daily) or placebo for 96 weeks*.

• Vitamin E group had significant improvement in global histology scores compared with placebo (43% vs 19%).

• Concerns regarding Vitamin E and increased mortality have led many Hepatologists to not recommend Vitamin E or to use 400 IU daily.


A New Kind of Coffee Connection!

Mechanism of Protective Effect of Coffee Unknown

• Caffeine, cafestol and kahweol protective in experimental studies

• Antioxidant effect

• Insulin sensitizing effect

• Coffee drinkers have higher levels of plasma adiponectin

Voltaire (1694 – 1778) 83 years

1. Who is this person and how old was he when he died?
2. How many cups of coffee did he drink every day?

50-72 !
More than 1 Billion People in the World Have Chronic Liver Disease

Consuming two cups of coffee per day reduces hospitalization rate and mortality from chronic liver disease by more than 50%


References: Coffee and Liver Disease, 2012
Sanjiv Chopra, MD, MACP


Large prospective study; Coffee consumption inversely associated with total and cause-specific mortality.

Potential Approaches to Treatment in the Future

• Will likely include combination therapy and life-style changes.

• Experimental study in a rat model of NASH combining angiotensin II receptor blocker with an oral iron chelator attenuated progression.

• Moderate exercise and coffee consumption likely of benefit.

Patients with Elevated Transaminases are not at Higher Risk for Statin Hepatotoxicity

<table>
<thead>
<tr>
<th>Mild-Moderate Elevation</th>
<th>Severe Elevation</th>
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<tbody>
<tr>
<td>1439 with normal transaminases prescribed a statin</td>
<td>1.9%</td>
</tr>
<tr>
<td>342 with elevated transaminases prescribed a statin</td>
<td>4.7%</td>
</tr>
<tr>
<td>2245 with elevated transaminases not prescribed a statin</td>
<td>6.4%</td>
</tr>
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Chalasani et al: Gastroenterology 2004;126

Quiz Answer True or False

1. NAFLD is the most common hepatic disorder in the U.S.

2. Serum ferritin is elevated in 50% of pts with NASH.

3. NASH has been reported in children.

4. Progression to cirrhosis occurs in 15-20% of pts.

5. NASH is likely the leading cause of cryptogenic cirrhosis.

6. The histologic features of NASH maybe seen in Wilson’s disease.

7. Both Amiodarone and Tamoxifen can cause NASH.

8. Primary hepatocellular carcinoma has been reported in patients with NASH and cirrhosis.