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.
Nonalcoholic Fatty Liver Disease: The Burgeoning Epidemic

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)

lobular sinusoidal neutrophils

Ballooning degeneration
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

ARS Question # 1

Choose the correct answer:

A. Non-alcoholic fatty liver disease (NAFLD) is estimated to afflict 40 million Americans.
B. 50% of patients with NAFLD evolve into cirrhosis of the liver.

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

ARS Question #2

Answer True or False (A is True, B is False):

Patients with NASH and a persistently normal ALT (defined as a normal ALT on 3 consecutive occasions over a 6 month period) do not have significant fibrosis on liver biopsy.

Patients with NASH

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

Fracanzani AL, et al.  
Hepatology 2008:48:792
Other Conditions Associated with NASH

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

One disorder that is critical to exclude in young individuals is Wilson’s disease.

K-F Ring
Drugs Associated with NASH

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

Progression to Cirrhosis 10 Yr Survival

<table>
<thead>
<tr>
<th>Condition</th>
<th>Progression to Cirrhosis</th>
<th>10 Yr Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcoholic Hepatitis</td>
<td>38 –50%</td>
<td>20%</td>
</tr>
<tr>
<td>NASH</td>
<td>8 – 26%</td>
<td>60%</td>
</tr>
</tbody>
</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

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>* NASH is a histologic dx</td>
<td>* Small but finite risk of complications</td>
</tr>
<tr>
<td>* Poor correlation between lab findings and histologic severity</td>
<td>* Biopsy results may not change management</td>
</tr>
<tr>
<td>* Biopsy results may change management</td>
<td>* Limited manpower</td>
</tr>
</tbody>
</table>

Suspected NASH: Reasonable to perform liver biopsy

If any of following present

- Peripheral stigmata of chronic liver disease
- Splenomegaly
- Cytopения
- 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?

Sampling error of liver biopsy

Fibrosis area: 65%

Fibrosis area: 15%

Courtesy of M. Pinzani, Florence

Fibrotest (fibrosure)

Alpha 2 macroglobulin, haptoglobin,
gammaglobulin, GGT, total bilirubin,
apolipoprotein A1

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

Am J Gastroenterol 2006

Fibrosure. 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

Courtesy of N. Afdhal, MD

---

Hepatic Elastography

- Fibroscan is a rapid and non-invasive measure of hepatic stiffness
- Hepatic stiffness correlates with fibrosis

The probe induces an elastic wave through the liver
The velocity of the wave is evaluated in a region located from 2.5 to 6.5 cm below the skin surface

Sampled volume: 1: 500

Courtesy N. Afdhal, MD

---

Sampling

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

Transient elastography (Fibroscan) is accurate in most patients with NAFLD. With high negative predictive value and modest positive predictive value, Fibroscan is useful as a screening test to exclude advanced fibrosis.

Wong V W-S, et al.
Hepatology 2010; 51:454-462

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%

Copyright © 2013 by Joslin Diabetes Center, Inc. All rights reserved. These materials may be used for personal use only. Any distribution or reuse of this presentation or any part of it in any form for other than personal use without the express written permission of Joslin Diabetes Center is prohibited.
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

Pathogenesis of NAFLD/NASH

The “Two Hit Hypothesis

1st “Hit”
- Hyperinsulinemia
  - ↑ FFA flux
  - ↓ FFA oxidation
  - ↓ Triglyceride export

2nd “Hit”
- ↑ Oxidative stress (Iron, CYP2E1)
- ↑ Lipid peroxidation
- ↑ TNFa
- ↑ TGFb
- ↑ Leptin

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, inflammation)
   • Improvement in insulin resistance
   • Higher Adiponectin levels
   Harrison SA, et al. 
   Hepatology 2009;49:80

2. Following bariatric surgery, Hepatic Fibrosis improved or was reversed in 66%.
   Furuya CK Jr., et al. 
   J Gastro Hepatol 2007;22:510

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.

1. Who is this person and how old was he when he died?
   Voltaire (1694 – 1778) 83 years

2. How many cups of coffee did he drink every day?
   50-72!

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
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.

“Coffee is so good, the infidels should not have exclusive use of it.”

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

<table>
<thead>
<tr>
<th></th>
<th>Mild-Moderate Elevations</th>
<th>Severe Elevations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1439 with normal transaminases prescribed a statin</td>
<td>1.9%</td>
<td>0.2%</td>
</tr>
<tr>
<td>342 with elevated transaminases prescribed a statin</td>
<td>4.7%</td>
<td>0.6%</td>
</tr>
<tr>
<td>2245 with elevated transaminases not prescribed a statin</td>
<td>6.4%</td>
<td>0.4%</td>
</tr>
</tbody>
</table>

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.

Quiz (Continued)  Answer True or False

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.