Evaluation and Treatment of Non-Alcoholic Fatty Liver Disease

The Skinny on Fatty Liver

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Relevant Financial Relationship(s)
List: None

Off Label Usage
List: None
2009–2010, over 78 million U.S. adults and 12.5 million U.S. children/adolescents were obese.

Among Obese Adults:
- Steatosis: 70-93%
- NASH: 9-30%
- Cirrhosis: 7-16%

12-23 million
5-12 million
In addition…

**IN 2011: 25.8 million children and adults have diabetes**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
<th>Estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steatosis</td>
<td>50-62%</td>
<td>7-9 million</td>
</tr>
<tr>
<td>NASH</td>
<td>30-36%</td>
<td>1-2.5 million</td>
</tr>
<tr>
<td>Adv fibrosis</td>
<td>5-9%</td>
<td></td>
</tr>
</tbody>
</table>

And … Among “healthy” Asx adult population

San Antonio, Texas (Williams et al, Gastroenterology 2011;140:124-31)

Dallas Heart Study Prevalence Numbers (Browning et al, Hepatology 2004;40:1387-95)

NASH prevalence among ethnic groups

Overall 12.2
Hispanic 19.4
Caucasian 9.8
African American 13.5
Other 6.7

N=40/328
N=14/72
N=20/265
N=5/37
N=1/14
Present and Future Demand for Liver Transplantation for NAFLD/NASH

Currently 1.1/million/year undergo liver transplantation for NAFLD.
- Frequency will increase to 2.4-4.0 /million/year 10-15 years

Charlton. Clin Gastro & Hep 2005
Fatty liver: DDx & Definitions

Steatosis: Simple fatty infiltration of the liver (NAFLD)

Steatohepatitis: Fatty infiltration with assoc. inflammation and fibrosis (NASH)

Non-Alcoholic = < 20 g EtOH/day

Large-droplet (macrovesicular) fat
- Alcohol
- Adult-onset diabetes mellitus
- Obesity
- Kwashiorkor
- Protein-calorie malnutrition
- Systemic illness (such as tuberculosis)
- Jejunoileal bypass
- Gastroplasty
- Hyperalimentation
- Drugs
  - methotrexate
  - corticosteroids
  - estrogens (high-dose)
  - amiodarone

Small-droplet (microvesicular) fat
- Reye’s syndrome
- Acute fatty liver of pregnancy
- Tetracycline toxicity
- Valproic acid toxicity
- Alcoholic foamy degeneration
- Non-A, non-B hepatitis
Alcohol

1 pony = 1 ounce
1 jigger/bar glass = 1 1/2 ounces
1 shot (*) = 1 1/2 ounces
1 snit = 3 ounces
1 wineglass = 4 ounces
1 split = 6 ounces
1 cup = 8 ounces
1 pint (pt) = 16 ounces
1 quart (qt) or liter = 32 ounces
1 fifth = 25.6 ounces (1/5 gallon)
1 gallon (gal)= 128 ounces

- Units / week
  7-14 👉
  21-28 👈

- 4oz wine, 12oz beer, 1-1.5 oz spirit
Obesity Focus
BMI is a Poor Marker for Obesity

BMI 33

6’5” 275 lb

6’1”, 242 lb
25 lb fluid
Not all obese patients have NASH…

% BMI >30 kg/m²

NASH

Crypto

ALD

HCV

PBC/PSC

Malik. AJT 2009
How does it happen?

Hyperailmentation effects are well known
Why doesn’t every obese patient get NASH?

(At least) Five Hits

- Overnutrition
- Insulin resistance
- Steatosis
- FFA
- Oxidative stress
- Mito injury
- Lipopoptosis
- Stellate cell Activation
- Fibrosis
Other Possible mechanisms of susceptibility to NASH with Progressive Fibrosis

Endocrine

Parents

Genes

Environment
Other Possible mechanisms of susceptibility to NASH with Progressive Fibrosis

- Endocrine
- Parents
- Genes
- Environment
PNLPLA3 Genotype and Histology

N=1117

- Steatosis: HR=1.46
- Inflammation: HR=1.83
- Fibrosis: HR=1.96

P<0.0001 all

Liang Hepatology 2010
Other Possible mechanisms of susceptibility to NASH with Progressive Fibrosis

- Endocrine
- Parents
- Genes
- Environment
A Fast Food Diet can Induce Steatohepatitis and Fibrosis

So What??....NAFLD/NASH increases risk of death over long term followup

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignancy</td>
<td>30</td>
</tr>
<tr>
<td>IHD</td>
<td>25</td>
</tr>
<tr>
<td>CHF</td>
<td>4</td>
</tr>
<tr>
<td>CVA</td>
<td>2</td>
</tr>
<tr>
<td>AAA</td>
<td>2</td>
</tr>
<tr>
<td>Liver</td>
<td>13</td>
</tr>
<tr>
<td>Infection</td>
<td>11</td>
</tr>
</tbody>
</table>

Adams. Gastro. 2005
# Fatty Liver

**Is a Risk Factor for CAD**

<table>
<thead>
<tr>
<th>Variable</th>
<th>( P ) value</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatty liver</td>
<td>(&lt;0.001^{**})</td>
<td>8.48 (4.39–16.40)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.002^{**}</td>
<td>2.94 (1.47–5.91)</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.014^{*}</td>
<td>2.31 (1.19–4.48)</td>
</tr>
<tr>
<td>HTN</td>
<td>0.109</td>
<td>1.63 (0.90–2.98)</td>
</tr>
<tr>
<td>LDL</td>
<td>0.102</td>
<td>0.99 (0.98–1.00)</td>
</tr>
</tbody>
</table>

![Intraluminal Thickness](image)

Targher, NEJM 2010

![Non-DM STEMI](image)

Boddi, Eur J Clin Inv 2013

Mirbagheri Liver Int. 2007
Implications are Huge

• “benign” fatty liver disease may not exist
• MS, NAFLD/NASH and cardiovascular disease are interwoven
• Future liver transplant candidates are significant risk of not being candidates due to underlying CVD
• Transplant patients are at even HIGHER risk of MS and CVD after transplant
Clinical Presentation

- Asymptomatic AbN LE, or abN imaging
- Hepatomegaly, in up to 50 % in different studies.
- Jaundice, edema, asterixis, and signs of portal hypertension occur in those with advanced cirrhosis.
- Muscle wasting may occur as the liver disease becomes more advanced but is often underestimated due to edema and preexisting obesity.
Lab features

• Common:
  • <10 X ALT/AST, Alk Phos elevated in 1/3, GGT elevated frequently
  • N alb, bili, INR
  • Elevated ferritin 53-62%
  • Hi lipids, glucose

• Less common:
  • Low titre ANA (<1:320), IgA elevation
  • Elevated transferrin saturation

significant liver disease can be seen in those with NAFLD and normal liver enzymes
Diagnostics

Hepatic imaging lacks sensitivity for minor amounts of steatosis (ie, less than 33% of hepatocytes)

• U/S sensitivity 83 %
  specificity 100 %
• CT sensitivity 54%
  specificity 95 %

Ramesh. Hepatology 2005
Limitations of US-Based Transient Elastography - Fibroscan

Limited depth penetration (obesity, ascites)
1-D approach with potential sampling errors
How Can We Manage NASH??
Management

**Lifestyle:**
- 10% of baseline weight at a rate of 1 to 2 lb/wk.
  - Caloric restriction
  - Decrease in saturated fats with total fats to <30% or less of total calories.
- Both intermittent as well as daily exercise can help achieve weight loss and improve **insulin** sensitivity.
- Hemoglobin A1c should ideally be brought to <7 percent, cholesterol control

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Ueno et al. *J. Hep.*, 27: 1997 **BMI** down by 3 resulted in **LE**, FBG normalized…Steatosis, inflammation and fibrosis all improved

Bacchi. Hep 2013
<table>
<thead>
<tr>
<th>Drug</th>
<th>No. of patients</th>
<th>Duration of treatment (m)</th>
<th>Biochemistry</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Choleretic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UDCA</td>
<td>24</td>
<td>12</td>
<td>Improved</td>
<td>Improved</td>
</tr>
<tr>
<td>UDCA + diet x 3</td>
<td>85</td>
<td>6</td>
<td>Improved</td>
<td>n/a</td>
</tr>
<tr>
<td><strong>Lipid Lowering</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clofibrate</td>
<td>16</td>
<td>12</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td><strong>Antioxidants</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Betaine</td>
<td>8</td>
<td>12</td>
<td>Improved</td>
<td>Improved</td>
</tr>
<tr>
<td>NAC</td>
<td>11</td>
<td>3</td>
<td>Improved</td>
<td>n/a</td>
</tr>
</tbody>
</table>

Atorvastatin— improved histology and biochem (Georgescu. J Gastrointestin Liver Dis. 2007)
Pioglitazone for NASH – NIH CRN PIVENS

Authors’ conclusions:
“Vitamin E is superior to placebo. No benefit of pioglitazone over placebo for the primary outcome (improvement in NASH).”

Sanyal. NEJM 2010
Optimizing Metabolic Syndrome

• Treat as normally indicated

• **ACE Inhibitor, Angiotensin receptor blockers** reduced steatosis, inflammatory cytokines and fibrosis in rats & humans

• **Fish Oil.** Animal models improves histologic steatosis and NASH.

  Improves insulin sensitivities.

  Anti-inflammatory, reduced ox stress.

Table 7. Doubling of ALT in NAFL/NAFLD and Hepatitis C Patients: Normal ALT Versus Elevated ALT at the Baseline

<table>
<thead>
<tr>
<th>Baseline ALT</th>
<th>Week</th>
<th>Pravastatin</th>
<th>Placebo</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAFL/NAFLD group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal ALT</td>
<td>12</td>
<td>5/45 (11%)</td>
<td>3/40 (7.5%)</td>
<td>0.6575</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>5/45 (11%)</td>
<td>4/40 (10%)</td>
<td>0.9849</td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>12</td>
<td>3/58 (5.2%)</td>
<td>4/61 (6.6%)</td>
<td>0.7203</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>4/58 (6.9%)</td>
<td>8/61 (13.1%)</td>
<td>0.2316</td>
</tr>
<tr>
<td>Chronic hepatitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal ALT</td>
<td>12</td>
<td>0/17 (0%)</td>
<td>1/16 (6.3%)</td>
<td>0.3173</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>0/17 (0%)</td>
<td>1/16 (6.3%)</td>
<td>0.3173</td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>12</td>
<td>0/21 (0%)</td>
<td>1/27 (3.7%)</td>
<td>0.3833</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>2/21 (9.5%)</td>
<td>5/27 (18.5%)</td>
<td>0.3810</td>
</tr>
<tr>
<td>All subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal ALT</td>
<td>12</td>
<td>5/73 (7.1%)</td>
<td>6/68 (8.8%)</td>
<td>0.5675</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>5/73 (7.1%)</td>
<td>7/68 (10.3%)</td>
<td>0.3700</td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>12</td>
<td>4/87 (4.6%)</td>
<td>5/92 (5.4%)</td>
<td>0.7363</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>7/87 (8%)</td>
<td>13/92 (14.1%)</td>
<td>0.2098</td>
</tr>
</tbody>
</table>

Lewis. Hepatology 2007
NASH Management new studies:

• **Caffeine from regular coffee** associated with reduce fibrosis progression (not so for espresso) OR 0.75, p= 0.034

• **Probiotics +/- prebiotics** 3 very small RCT of 8-12 weeks probiotics reduced liver enzymes
  (Aller. EurRevMed Pharm 2011,
  Vajro. J Ped Gastro Nutr 2011,
  Wong. Ann Hep 2013)

….. More studies needed
Surgical Weight Loss

• 19/23 (82%) NASH pt, significant histologic improvement after losing 34 +/- 17 kg with gastric band

• Roux-y-gastric bypass – 82-85% improvement in inflammation, 39-75% improved fibrosis

• monitor for signs of liver dysfunction during weight loss
Bariatric Surgery in Cirrhotic Patients

Mortality

<table>
<thead>
<tr>
<th>Multivariate</th>
<th>AdjOR</th>
<th>(95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No cirrhosis (Ref, n=670 950)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compensated cirrhosis (n=3888)</td>
<td>2.2</td>
<td>(1.0–4.6)</td>
<td>0.041</td>
</tr>
<tr>
<td>Decompensated cirrhosis (n=62)</td>
<td>21.1</td>
<td>(5.4–82.3)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

42% perioperative mortality in decompensated cirrhotic at low volume (<50/year) centers despite predominantly only restrictive procedures

An Approach..

6 months weight loss (15-20kcal/kg/d, 30-45g fat/d, exercise)

LE < 2x N or decreasing – con’t weight loss efforts, observe 6-12 mo

LE > 2x N or increasing – consider a study, consider liver biopsy for staging (and incentive)

DM – metformin, ‘glitazones, > insulin

Lipids - Statins, fibrates, Fish oil

HTN – ACEI/A2B benefit in NASH

BMI>35 consider bariatric surgery
Take a moment....