The Skinny On Non Alcoholic Fatty Liver Disease

UCSF Advances in Internal Medicine

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Non Alcoholic Fatty Liver Disease: Outline

- Pathogenesis
- Epidemiology
- Diagnosis
- Hepatology Referral?
- Management Options
Causes of Fatty Liver

Drugs and Toxins
- ALCOHOL
- Corticosteroids
- Tamoxifen
- Amiodarone
- Industrial solvents

Nutritional Syndromes
- JI Bypass
- TPN
- Rapid weight loss

Inherited Metabolic Diseases
- Lipodystrophy
- Abetalipoproteinemia
- Wilson’s Disease

Causes of Non Alcoholic Fatty Liver Disease (NAFLD)

Drugs and Toxins
- Alcohol
- Corticosteroids
- Tamoxifen
- Amiodarone
- Industrial solvents

Nutritional Syndromes
- JI Bypass
- TPN
- Rapid weight loss

Inherited Metabolic Diseases
- Lipodystrophy
- Abetalipoproteinemia
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Metabolic Syndrome
- IR/DM
- Obesity
- Dyslipidemia
- Hypertension
Emerging Risk Groups for NAFLD

- Hypothyroidism
- Obstructive Sleep Apnea
- Hypogonadism
- Hypopituitarism
- Polycystic Ovarian Syndrome

Fat Accumulation in the Liver

*Increased fatty acid influx from adipose tissue*
  - Hyperinsulinemia
  - Obesity
  - Diet

*Decreased fatty acid oxidation*
  - Hyperinsulinemia
  - Genetic
  - Leptin deficiency/resistance

*Increased fatty acid synthesis*
  - Hyperinsulinemia
  - Excess carbohydrate feeding
  - Leptin deficiency/resistance

Triglycerides
Obesity Trends Among U.S. Adults

1990

BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person

No Data           <10%          10%–14%  

Obesity Trends Among U.S. Adults

2000

No Data          <10%          10%–14%  

15%–19%          ≥20%
Obesity Trends Among U.S. Adults
2010

Epidemiology

• What is the prevalence of NAFLD in general population?
  30%
• Prevalence of NAFLD in morbid obesity?
  80%
• Prevalence of NAFLD in DM2?
  70%
• Prevalence of NAFLD in hyperlipidemia?
  50%

NAFLD = Hepatic Manifestation of the Metabolic Syndrome

Chalasani et al., Am J Gastro 2012
NAFLD: Non Alcoholic Fatty Liver Disease

NAS: Non alcoholic steatosis
NASH: Non alcoholic steatohepatitis

Fat + Inflammation ± Fibrosis

Fat ± Inflammation ± Fibrosis

Cirrhosis ± Inflammation ± Fat

Pathogenesis of NAFLD/NASH:

Multi-Hit Hypothesis

Normal → Steatosis  → Inflammation & Fibrosis

1st “Hit”
- Insulin resistance
  - Lipolysis
  - FFA flux
  - Triglyceride export

2nd “Hit”
- Oxidative stress
  - Lipid peroxidation
  - Cytokines

CULPRITS?
- Genetic
- Dietary
- Microbiome
Pathogenesis of NAFLD/NASH - The Multi-Hit Hypothesis

Natural History

NAFLD 30% → NASH 5-15% → Progressive Fibrosis

25-30% over 5-6 yrs

10-30%, ~ 1 stage every 7 years

Cirrhosis related complications:
- ESLD
- HCC
- Need for LT

40-60% over 5-7 yrs

NASH Cirrhosis

Implications of NAFLD

NASH Cirrhosis

Within 10 years will be leading cause of:
1) End Stage Liver Disease
2) Liver Cancer
3) Liver Transplant

Charlton et al., Gastro 2011
Obesity and HCC-related Mortality

<table>
<thead>
<tr>
<th>BMI Range</th>
<th>Death Rate per 100K</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>35 to 39</td>
<td>8</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>30 to 34.5</td>
<td>6</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>20 to 20.9</td>
<td>5</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>18.5 to 25</td>
<td>5</td>
<td>9</td>
<td>5</td>
</tr>
</tbody>
</table>

- N= 900,000 cancer free at enrollment
- Followed for 16 yrs
- N= 57,145 new cancers

What is the most common cause of death in patients with NAFLD?

A. Cirrhosis with portal hypertensive complications
B. Hepatocellular carcinoma (HCC)
C. Cardiovascular disease
What is the most common cause of death in patients with NAFLD?

1. Cirrhosis with portal hypertensive complications
2. Hepatocellular carcinoma (HCC)
3. Cardiovascular disease

Mortality in NAFLD

- NHANES III
- Eligible: 12,822 (817 NAFLD)
- F/U: 8.7 yrs (median)

Causes of death in NAFLD:
1) CV
2) Malignancy
3) Liver

Ong et al. J Hepatology 2008
Independent Risk Factors for Clinically Significant CAD

- N=317 elective coronary angiogram
- N=85 Normal or mild CAD and N=232 Clinically relevant CAD

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatty Liver</td>
<td>8.48</td>
<td>4.39-16.40</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.54</td>
<td>1.47-5.91</td>
<td>0.002</td>
</tr>
<tr>
<td>Male Sex</td>
<td>2.31</td>
<td>1.19-4.48</td>
<td>0.014</td>
</tr>
<tr>
<td>HTN</td>
<td>1.63</td>
<td>0.90-2.98</td>
<td>0.106</td>
</tr>
<tr>
<td>LDL</td>
<td>0.99</td>
<td>0.99-1.00</td>
<td>0.201</td>
</tr>
</tbody>
</table>

*Miraghi et al. Liver Internat. 2007*
Diagnosis of Non-Alcoholic Fatty Liver Disease

Abdominal imaging with steatosis (+/- elevated liver enzymes) +

Other causes of CLD excluded +

Usually with clinical evidence of metabolic syndrome

Detecting the Presence of Steatosis

Advantages:
- Widely available
- Inexpensive
- Painless

Limitations:
- Lacks sensitivity
  - Requires 30% steatosis

- Bright liver
- Echotexture - increased compared to kidney
- Vascular blurring
Steatosis on MRI

- Detects even mild steatosis
- Evolving technology with improved sensitivity: ie MR spectroscopy, Proton-Density Fat-Fraction (PDFF)
- Good research tool for longitudinal studies of steatosis

Incidentally Detected Steatosis By Imaging in Primary Care Setting:

1) Exclude alcohol and culprit meds (heavy alcohol: > 21 drinks in men or > 14 drinks in women weekly)
2) Evaluate for Metabolic Syndrome: DM, HTN, obesity, HL
3) Perform liver tests: bilirubin, AST, ALT, alk phos

- Elevated Liver Tests (check HBV/HCV Abs)
- Hepatology Referral (unless alcohol clear culprit then counsel re reduction)
- Normal Liver Tests
- Repeat Liver Tests Yearly*

*Not data driven
What would a hepatologist order?

*Guided by history, presentation, and pattern of injury, not shotgun approach:*

- AMA, IgM (for PBC)
- ASMA, ANA, IgG
- A1AT phenotype
- Iron, Tsat, ferritin
- HAV Ab (for vaccination)
- HBsAg, sAb, cAb
- HCV Ab
- Ceruloplasmin age < 45
- HgAIC
- Fasting lipids

54 y/o M with diabetes, hyperlipidemia, HTN and morbid obesity. Ultrasound notes diffuse fatty infiltration. ALT 50, AST 45. ANA >1:160 and ASMA 1:40.

What is *most likely* cause of abnormal liver tests?

A. Autoimmune hepatitis
B. Autoimmune hepatitis plus NAFLD
C. 3) NAFLD
Question

• 54 y/o M with diabetes, hyperlipidemia, HTN and morbid obesity. Ultrasound notes diffuse fatty infiltration. ALT 50, AST 45. ANA >1:160 and ASMA 1:40.

What is *most likely* cause of abnormal liver tests?
1) Autoimmune hepatitis
2) Autoimmune hepatitis plus NAFLD
3) NAFLD

Autoantibodies in NAFLD

• Positive ANA > 1:160 or ASMA >1:40 were present in **21%** of patients with NAFLD

• Positive AMA can be seen in **8%** patients with NAFLD

• Autoimmune markers are not associated with more advanced histology

Vuppalanchi R et al., Hepatol Int 2011
When to Biopsy?

• To exclude other types of liver disease

• If atypical phenotype: NAFLD in absence of metabolic risk factors

• To confirm stage of fibrosis in those at increased risk for advanced disease: age > 45, DM, obesity, AST/ALT > 1, ALT > 3-5x ULN

• To diagnose NASH prior to pharmacotherapy

• To support major therapeutic decision – ie bariatric surgery, clinical trials

Limitations of Liver Biopsy

• Underestimating fibrosis

• Inter and intra-observer variability

• Limited measurements

Non invasive measures of fibrosis.....

Colloredo G, J Hepatol 2003; Bacchetti P, BMC Infect Dis 2007; Brunetti E, J Hepatol 2004
## NAFLD Fibrosis Scoring Systems

### Table 1 | Predicting advanced fibrosis (F3–4) using routine clinical and laboratory variables in patients with NAFLD

<table>
<thead>
<tr>
<th>Predictive score</th>
<th>Patients (n)</th>
<th>Variables/formula [units]</th>
<th>AUROC (95% CI)</th>
<th>Cut-off points</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAFLD fibrosis score(^{50})</td>
<td>733</td>
<td>(-1.675 + 0.037 \times \text{age [years]} + 0.094 \times \text{BMI [kg/m}^2] + 1.13 \times \text{HbA1c/diabetes [yes = 1, no = 0]} + 0.99 \times \text{AST:ALT ratio} - 0.013 \times \text{platelet count} \times 10^9/\text{l} - 0.66 \times \text{albumin [g/dl]})</td>
<td>0.88 (0.85–0.92)</td>
<td>≤-1.455</td>
<td>56</td>
<td>93</td>
</tr>
<tr>
<td>BARD score(^{54})</td>
<td>827</td>
<td>(0.4184 \times \text{glucose [mmol/l]} + 0.0701 \times \text{ALT [U/l]} + 0.00006 \times \text{ferritin [µg/l]} - 0.0102 \times \text{platelet [g/l]} - 0.0260 \times \text{ALT [U/l]} + 0.0459 \times \text{body weight [kg]} + 0.0842 \times \text{age [years]} + 11.6226)</td>
<td>0.94</td>
<td>≤0.611</td>
<td>80</td>
<td>90</td>
</tr>
<tr>
<td>FibroMeter(^{\text{TM}}) NAFLDfibx</td>
<td>235</td>
<td>(0.7464 \times \text{sex [male sex = 1, female sex = 0]} + (0.10039 \times \text{alcohol [g/l]} + 0.0302 \times \text{hyaluronic acid [µg/l]} + 0.0891 \times \text{bilirubin [µmol/l]} - 0.0012 \times \text{GGT [U/l]})</td>
<td>0.814 (0.73–0.90)</td>
<td>0.37</td>
<td>57.1</td>
<td>92.4</td>
</tr>
</tbody>
</table>

**Limited Discrimination Between Intermediate Stages of Fibrosis**

Castera et al., Nat Rev Gastroenterol Hepatol 2013

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### Magnetic Resonance Elastography

- **Simple Steatosis**
- **Inflammation Without Fibrosis**
- **Fibrosis**

*Courtesy of S. Harrison*
Transient Elastography (Fibroscan®)

- FDA approved in 2009 for staging liver fibrosis
- US-based probe transmits vibrations through liver: velocity correlates with degree of scarring
- Validated for all stages of NAFLD related scarring
- Painless, quick, performed at bedside
- XL probe facilitates use in obese patients

SCREENING

**AASLD Says:**
- Family members: No data to support
- Metabolic syndrome: Insufficient data to support

**I recommend:**
- Family members: No data to support
- Metabolic syndrome: Yes - particularly those with obesity and diabetes

AASLD Guidelines 2012
55 yo man with fatty liver and obesity, but no diabetes. Liver biopsy consistent with steatohepatitis and stage 2 fibrosis. Besides lifestyle modification what medical therapy is recommended?

A. Metformin  
B. Pioglitazone  
C. Vitamin E  
D. Pentoxifylline  
E. No additional treatment
Question

55 yo man with fatty liver and obesity, but no diabetes. Liver biopsy consistent with steatohepatitis and stage 2 fibrosis. Besides lifestyle modification what is therapy is currently recommended?

- Metformin
- Pioglitazone
- Vitamin E
- Pentoxifylline
- No treatment

Lifestyle Modification

Exercise:

- Moderate intensity aerobic activity 3-6 times per week for 1-3 months → no weight change but:
  - Improved AST/ALT
  - Decreases hepatic fat on imaging
  - No data on histologic benefits
  - Long term maintenance difficult

Thoma C et al., J Hepatol 2012, Review
Dietary Modification

- Ideal NAFLD diet not clear: Mediterranean, Paleo, Common sense?
- Saturated fat and fructose stimulate hepatic lipid deposition
- Low-mod fat restriction with mod-high carb restriction for 1-6 months 4-14% decreased weight
- Associated with improved AST/ALT, less insulin resistance, less fat on imaging
  - Limited data on histologic benefits

Thoma C et al., J Hepatol 2012 (Review)

"Not all fat’s bad. Maybe you’re gaining the omega-3 polyunsaturated kind."
Bariatric Surgery

- **Criteria:**
  - BMI $\geq 40 \text{ kg/m}^2$
  - BMI 35-40 kg/m$^2$ with significant comorbidities (DM, sleep apnea, HTN)
  - Failed other medically-managed weight loss programs
  - *15,000,000 adults in U.S. meet criteria*

- **Efficacy:**
  - 60-70% weight loss (60-250+ lbs/1-2yrs)
  - Best medical regimens achieve 10-25 lb weight loss

Bariatric Surgery & NASH

*Caveats*

- Operative morbidity/mortality
- Malnutrition
- Rapid weight loss
  - Increased liver enzymes
  - Worsening portal inflammation & fibrosis
  - Acute/subacute liver failure

*Good option in select candidates with advanced fibrosis at UCSF after hepatology evaluation*
MEDICATIONS

Targeting Treatment for NASH
PIVENS Trial: Pioglitazone, Vitamin E, or Placebo for Non Alcoholic Steatohepatitis

- RTC: Adults with biopsy proven NASH

- Excluded DM and cirrhosis

- Randomized to pioglitazone (n=80), Vitamin E (n=84), or placebo (n=83) for 2 years

- $1^\circ$ endpoint = Improved composite histologic score

- $2^\circ$ endpoints = Improved histologic components, anthropomorphic measures, lipids

Sanyal et al, NEJM 2010

PIVENS

Histologic Improvement in NASH*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>% Improved</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>19%</td>
<td>0.04</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>34%</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Decrease in NAS by ≥ 2 pts with ≥1 point decrease in ballooning.

Sanyal et al, NEJM 2010
PIVENS
Conclusions

• Vitamin E superior to placebo for treatment of NASH in adult, non-diabetic patients

• Pioglitazone
  – Did not meet primary endpoint
  – Superior to placebo in improving other key histological features and liver enzymes
  – Resulted in weight gain

• Neither drug improved fibrosis score over duration of study

Sanyal et al, NEJM 2010

Pioglitazone in NASH

• Side effect profile may limit use
  – CV events, CHF, weight gain, bladder cancer, bone fractures in women
• Longterm safety and efficacy in NASH unknown

Aliment Pharmacol Ther. 2012
Empiric Vitamin E for Suspected NASH?

- 70-75% have isolated hepatic steatosis
- 50% of patients don’t respond to Vitamin E
- Increased risk for hemorrhagic stroke (RR 1.22 (95% CI 1.00-1.48))
- Prostate cancer risk...


Vitamin E and the Risk of Prostate Cancer
The Selenium and Vitamin E Cancer Prevention Trial (SELECT)

Figure 2. Cumulative Incidence of Prostate Cancer

HR 1.17. p=0.008

Klein et al. JAMA 2011
### Pentoxifylline Improves Nonalcoholic Steatohepatitis: A Randomized Placebo-Controlled Trial

Claudia O. Zein, Lisa M. Verian, Premma Gogate, Rocio Lopez, John P. Kirwan, Ariel E. Feldstein, and Arthur J. McCallough

<table>
<thead>
<tr>
<th>Condition</th>
<th>Pentoxifylline N=26</th>
<th>Placebo N=29</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAS decrease of &gt;2 points (ITT)</td>
<td>10 (38.5%)</td>
<td>4 (13.5%)</td>
<td>0.036</td>
</tr>
<tr>
<td>Steatosis</td>
<td>15 (75%)</td>
<td>5 (19%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lobular inflammation</td>
<td>11 (55%)</td>
<td>6 (23%)</td>
<td>0.026</td>
</tr>
<tr>
<td>Ballooning</td>
<td>6 (30%)</td>
<td>6 (23%)</td>
<td>0.60</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>7 (35%)</td>
<td>4 (15%)</td>
<td>0.17</td>
</tr>
<tr>
<td>Mean change in fibrosis score</td>
<td>-0.2</td>
<td>+0.4</td>
<td>0.038</td>
</tr>
</tbody>
</table>

Zein et al. Hepatology 2012

### The FLINT trial

- Obeticholic acid (OCA) = potent activator of farnesoid X nuclear receptor reduces liver fat and fibrosis in animal models of NAFLD
- N = 283 patients randomized at 8 centers to OCA 25mg daily vs placebo
- 72 weeks of treatment
- Primary endpoint = Improvement in NAFLD activity score ≥ 2 + no worsening of fibrosis

Neuschwander-Tetri et al. Lancet 2015
FLINT summary

• OCA significantly improved all histological features of NASH

• OCA was associated with pruritus in 23%

• OCA was associated with elevated total and LDL cholesterol and decreased HDL cholesterol

• Long term safety data needed

Neuschwander-Tetri et al. Lancet 2015

Available Therapeutic Options

• **Vitamin E**: FIRSTLINE
  • NASH without diabetes
  • Insufficient evidence to treat diabetics or cirrhotics

• **Pioglitazone**
  • NASH with or without diabetes
  • Limited data in cirrhotics

• **Pentoxifylline**
  • Promising
  • Need more data on ideal subpopulation

• **Other: Orlistat, Metformin** - can’t yet be recommended
Limitations of Available Drugs

- Effect size in all of these trials is small
- High placebo response rate
- No end point for stopping meds

NAFLD Summary

- NAFLD is most common cause of CLD: NASH will soon be the leading cause of cirrhosis, HCC, and need for LT
- For incidentally detected steatosis: perform liver tests and screen for metabolic syndrome
- #1 cause of death in NAFLD = CAD
- Patients with NAFLD and elevated liver enzymes should be evaluated by hepatology
• Steatosis is diagnosed by imaging, though diagnosis of NASH requires biopsy

• Vitamin E is first-line for biopsy confirmed NASH

• Lifestyle modification remains cornerstone:
  Goal weight loss 5-10% of body weight

• To date no medical therapy for NASH cirrhosis...

• Anti-fibrotic trials underway: goal to halt and reverse hepatic fibrosis

Thank You!

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