Fatty Liver, NASH: new diagnostics and new treatments

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HASLD

TP HCMC June 2016
NAFLD: the hepatic manifestation of the metabolic syndrome

120 million have metabolic syndrome
~80% have NAFLD
30% of US population has a fatty liver
3-5% have NASH
## Outcomes in NAFL-D

<table>
<thead>
<tr>
<th></th>
<th>Surrogates</th>
<th># Studies</th>
<th>OR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall Mortality</strong></td>
<td><strong>NAFLD vs. General Population</strong></td>
<td>8 studies</td>
<td>1.57 [1.18-2.10]</td>
</tr>
</tbody>
</table>
| **Incident CVD**   | • ALT as a surrogate  
                      | • GGT as a surrogate  
                      | 6 studies  
                      | 10 studies  
                      | 7 studies  
                      | 1.10 [0.85-1.41]  
                      | 1.57 [1.42-1.74]  
                      | 2.05 [1.81-2.31]  |
| **Incident type2 DM** | • ALT as a surrogate  
                      | • GGT as a surrogate  
                      | 17 studies  
                      | 12 studies  
                      | 3 studies  
                      | 1.97 [1.77-2.20]  
                      | 2.74 [2.39 – 3.14]  
                      | 3.51 [2.28-5.41]  |

Williams Annals of Internal Medicine  2011
A Disturbing Evolutionary Development
Prevalence of Self-Reported Obesity Among U.S. Adults by State and Territory, BRFSS, 2014

Prevalence estimates reflect BRFSS methodological changes started in 2011. These estimates should not be compared to prevalence estimates before 2011.

Source: Behavioral Risk Factor Surveillance System, CDC.
## Risk Factors for NAFLD

<table>
<thead>
<tr>
<th>Major Co-morbidities</th>
<th>Emerging Associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2 Diabetes</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>Sleep Apnea</td>
</tr>
<tr>
<td>Obesity</td>
<td>Hypopituitarism</td>
</tr>
<tr>
<td>Metabolic Syndrome</td>
<td>Polycystic Ovary Syndrome</td>
</tr>
</tbody>
</table>
Estimated fructose intake and weight trends in the U.S.

Fructose

- Dietary Carbohydrates can be converted to fat in the liver
- Fructose (alone or as part of sucrose) drives lipogenesis and promotes NAFLD
- Epidemiologic studies, clinical trials, and animal studies show that excess carbohydrate consumption contributes to NAFLD
- High fructose consumption depletes hepatic ATP and impairs recovery from ATP depletion
NAFLD and Ethnicity

• Hepatic TG content by MRS* in 2,287 subjects
• 32.1% White, 48.3% Black, 17.5% Hispanic
• One-third had hepatic steatosis
• 45% Hispanics, 33% Whites, 24% Blacks
• Most (79%) had normal serum ALT
• Steatosis related to IR, obesity in Hispanics
• Not related to these risk factors in Blacks
• Steatosis > Men:Women except in Blacks

*Browning et al. Hepatology. 2004 ;40:1387-95
NASH Prevalence Among Ethnic Groups

- Overall: 12.2% (N=40/328)
- Hispanic: 19.4% (N=14/72)
- Caucasian: 9.8% (N=20/205)
- African American: 13.5% (N=5/37)
- Other: 6.7% (N=1/14)

p=0.03
Key physiologic and microbiological features of the gut

500-1000 Microbial species

- **Aerobes**
  - Stomach: <10^2 cfu/mL, pH 1-2
  - Duodenum: 10^1-3 cfu/mL, pH 6-7
  - Jejunum: 10^3-4 cfu/mL, pH 6-7
  - Ileum: 10^7-9 cfu/mL, pH 6-7

- **Anaerobes**
  - Colon: 10^{10-12} cfu/mL, pH 5-7

**Digestion and acid secretion**

**Digestion and absorption of carbohydrates, proteins, and fats**

**Absorption of bile acids and vitamin B_{12}**

**Absorption of water, electrolytes, and short-chain fatty acids**

The intestinal microbiome modulates insulin resistance and metabolism
Before diet therapy, obese people had fewer Bacteroidetes ($P<0.001$) and more Firmicutes ($P=0.002$) than did lean controls.
Risk Factors for NAFL-Dis of NAFLD

Obesity, Genetics, Environment (bacteria), Diet, Activity
(Inulin sensitivity vs resistance)

↑ FFA

↓ Met clearance
Glucose

− Hepatic glucose output

↑ Glucose load

Hyperinsulinemia
Insulin Resistance in NASH

Stages of fatty disorders of liver
those with fatty liver rarely progress
to steatohepatitis

- Fatty liver
- Steatohepatitis
- Steatohepatitis + fibrosis
- Steatohepatitis + cirrhosis

Mortality: ~ 3%
Risk factors: age, diabetes, BMI

Hepatocellular cancer
IS NAFLD Progressive?

Consequences of NAFLD

- Normal
- Simple Steatosis
- NASH: 15%
- Cirrhosis
- HCC

By itself: Non-progressive

References:
Types of Fatty Liver Disease

NASH
- By itself: Benign
- Over 10 years: Cirrhosis
- 10%-20%

Steatosis alone (NAFL)
- By itself: Benign
Liver-Related and Overall Mortality in Patients with NAFLD

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Follow-up (mean, yrs)</th>
<th>Liver-related mortality</th>
<th>Overall mortality</th>
<th>Increased Mortality(\d)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Simple Steatosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Matteoni et al (1999)</td>
<td>49</td>
<td>9</td>
<td>2.0%</td>
<td>33.0%</td>
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<tr>
<td>Ekstedt et al (2006)</td>
<td>58</td>
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<td>No</td>
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<tr>
<td>Rafiq et al (2009)</td>
<td>74</td>
<td>19*</td>
<td>2.7%</td>
<td>56.8%</td>
<td>No</td>
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<tr>
<td>Soderberg et al (2010)</td>
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<td>21</td>
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<tr>
<td>Dam-Larsen et al (2009)</td>
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<td>28.2%</td>
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<tr>
<td><strong>Total/mean</strong></td>
<td>418</td>
<td>17</td>
<td><strong>1.7%</strong></td>
<td><strong>32.9%</strong></td>
<td></td>
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<tr>
<td><strong>NASH</strong></td>
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<tr>
<td>Matteoni et al (1999)</td>
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<td>8</td>
<td>10.0%</td>
<td>30.0%</td>
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<td>Ekstedt et al (2006)</td>
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<td>Rafiq et al (2009)</td>
<td>57</td>
<td>19*</td>
<td>17.5%</td>
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<td>Soderberg et al (2010)</td>
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<td>47.1%</td>
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<td>9</td>
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<td>15.0%</td>
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<tr>
<td>Adams et al (2005)</td>
<td>49</td>
<td>8</td>
<td>8.1%</td>
<td>35.0%</td>
<td>Yes</td>
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<tr>
<td>Younossi et al (2011)</td>
<td>131</td>
<td>10*</td>
<td>13.7%</td>
<td>21.3%</td>
<td>NR</td>
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<tr>
<td><strong>Total/mean</strong></td>
<td>349</td>
<td>11</td>
<td><strong>8.6%</strong></td>
<td><strong>34.1%</strong></td>
<td></td>
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<tr>
<td><strong>NAFLD-related cirrhosis</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Hui et al (2003)</td>
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<td>7</td>
<td>21.0%</td>
<td>26.0%</td>
<td>NR</td>
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<tr>
<td>Sanyal et al (2006)</td>
<td>152</td>
<td>10</td>
<td>14.5%</td>
<td>19.1%</td>
<td>NR</td>
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<td>Yatsuji et al (2009)</td>
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<td>Bhala et al (2011)</td>
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<td>13.4%</td>
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<td><strong>Total/mean</strong></td>
<td>490</td>
<td>7</td>
<td><strong>12.1%</strong></td>
<td><strong>24.3%</strong></td>
<td></td>
</tr>
</tbody>
</table>

Lomonaco & Cusi, 2012
Metabolic Syndrome and Its Hepatic Manifestation

Abdominal obesity
Glucose intolerance/insulin resistance
Hypertension
Atherogenic dyslipidemia
Proinflammatory/prothrombotic state

Diabetes
CVD
NAFLD
NASH

National Cholesterol Educational Program (NCEP), Adult Treatment Panel (ATP) III; 2001.
Pathogenesis of NASH
The Multi-hit Hypothesis

The Metabolic Syndrome

Insulin Resistance

1st hit
Normal Liver

2nd hit
Steatosis

3rd hit
NASH

Cytokines
Adipokines
Oxidative stress
Apoptotic pathways
Others

Fibrosis
Clinical Features of NAFL/NASH

**Symptoms:**
- Variable
- Vague (fatigue, malaise, RUQ discomfort)
- Mostly absent

**Signs:**
- Hepatomegaly common
- Splenomegaly in some
- Portal hypertension unusual

**Labs:**
- Increased AST, ALT typical
- ± increased Alk. Phos., GGT
- Increased cholesterol, triglycerides common
- Increased glucose common
- Viral markers (-)
- Autoantibodies (-)
- Iron studies abnormal sometimes

**Imaging:**
- Fatty liver
Work up of patients with NAFLD

- Imaging to establish the presence of steatosis
- Meticulous alcohol and medication history
- Exclusion of co-existing or competing etiologies
- Auto-antibodies and hyperferritenemia are common
- Fasting lipid profile and measures of insulin resistance
- Liver biopsy to establish the presence of NASH
How to establish diagnosis of NAFLD and identify patients with NASH?

- Patients with NAFLD or NASH are generally asymptomatic
- Clinical presentations cannot distinguish NASH
- Current radiologic modalities are unable to distinguish NASH or accurately detect fibrosis
- Non-invasive biomarkers are not established (getting closer)
- Therefore, in 2016, liver biopsy remains “the imperfect gold standard” to diagnosis and stage NASH
Histologic Progression of NASH

Stage 0  Stage 1  Stage 2  Stage 3  Stage 4

Courtesy of Goodman, Z
How to decide when to do a liver Bx

*NASH Practice Guidelines*

↑ ALT

Rule out other causes of liver disease

- Causes found
- No causes found

Metabolic syndrome present

- YES
- NO

Will Bx change Rx

- BX

Will Bx change Rx

- Yes
  - Discuss risks/benefits
  - Make patient aware of risks

- No
  - Of not doing Bx

Liver biopsy should be considered in patients with NAFLD who are at increased risk to have steatohepatitis and advanced fibrosis. (Strength – 1, Evidence - B)

The presence of metabolic syndrome and the NAFLD Fibrosis Score may be used for identifying patients who are at risk for steatohepatitis and advanced fibrosis. (Strength – 1, Evidence - B)

Liver biopsy should be considered in patients with suspected NAFLD in whom competing etiologies for hepatic steatosis and co-existing chronic liver diseases cannot be excluded without a liver biopsy. (Strength – 1, Evidence - B)
Surrogate Markers for NASH ± Advanced Fibrosis

- **Predict NASH**
  - Metabolic Syndrome
  - CK-18 fragments
  - CK-18 + sFas
  - Oxidized Fatty acids
  - NASH test
  - NASH Predictive Index
  - Obesity NAFLD score
  - NASH Clinical Score
  - NAFIC (ferritin, insulin, collagen)

- **Predict advanced fibrosis**
  - Fibrotest
  - NAFLD Fibrosis Score
  - BARD score
  - ELF
  - Fibrometer
  - OWL Genomics
  - IU panel
  - Transient elastography
  - MR elastography
**Clinical Factors that are different between Isolated Fatty Liver and NASH**

<table>
<thead>
<tr>
<th>Clinical Variable</th>
<th>Not NASH (n=89)</th>
<th>NASH (n=40)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>31.7 (5.3)</td>
<td>34.4 (5.4)</td>
<td>0.01</td>
</tr>
<tr>
<td>Fasting Insulin</td>
<td>14 (8.4)</td>
<td>23.2 (13)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>36.2 (15.7)</td>
<td>50.9 (19.6)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>25.6 (7.4)</td>
<td>36.3 (13.1)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>49.2 (15.7)</td>
<td>44.3 (9)</td>
<td>0.03</td>
</tr>
<tr>
<td>Adiponectin (ng/mL)</td>
<td>11028 (13078)</td>
<td>7815 (4811)</td>
<td>0.02</td>
</tr>
<tr>
<td>hsCRP (ng/mL)</td>
<td>5355 (5537)</td>
<td>7351 (6397)</td>
<td>0.04</td>
</tr>
<tr>
<td>K-18 (U/L)</td>
<td>210.3 (118)</td>
<td>307.1 (233.1)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*Williams CD, Gastroenterology 2011*
For every 50 U/L increase in plasma CK-18, the likelihood of having NASH increased 30%.

<table>
<thead>
<tr>
<th>K-18 level (U/L)</th>
<th>Sensitivity, % (95% CI)</th>
<th>Specificity, % (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>246</td>
<td>75 (64-83)</td>
<td>81 (61-93)</td>
</tr>
<tr>
<td>279</td>
<td>71 (60-80)</td>
<td>85 (65-96)</td>
</tr>
<tr>
<td>281</td>
<td>67 (57-77)</td>
<td>89 (70-98)</td>
</tr>
<tr>
<td>287</td>
<td>65 (54-75)</td>
<td>92 (75-99)</td>
</tr>
</tbody>
</table>

Changes in K-18 levels in PIVENS Trial

Vuppalanchi CGH 2014
NAFLD: sonographic evidence

- Bright liver
- Echotexture increased compared to kidney
- Vascular blurring
CT scan: fatty liver
Fat in the liver may be focal
NASH

Histology of NASH

Ballooning degeneration

Mallory’s hyalin
Non-alcoholic steatohepatitis
The Metabolic Syndrome

1. Cytokines
2. Adipokines
3. Oxidative stress
4. Others

Insulin Sensitizing Agents

Farnesoid-X Receptor Agonist

Lipid Lowering Agents

Weight Loss

Antioxidants

- Cytokines
- Adipokines
- Oxidative stress
- Others

Normal Liver → Steatosis → NASH → Fibrosis

1st hit → 2nd hit → 3rd hit
### Treatment: Weight Loss

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Intervention</th>
<th>Duration (months)</th>
<th>Design</th>
<th>ALT</th>
<th>Histology</th>
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<tr>
<td>Hickman</td>
<td>31</td>
<td>Diet</td>
<td>15</td>
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<td>+</td>
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<td>Huang</td>
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<td>Diet</td>
<td>12</td>
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<td>Palmer</td>
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<td>Diet</td>
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<td>Andersen</td>
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<td>Diet</td>
<td>4-23</td>
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<td>+/-*</td>
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<td>Diet/Ex</td>
<td>3</td>
<td>Open label</td>
<td>+</td>
<td>N/A</td>
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<td>Ueno</td>
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<td>Diet/Ex</td>
<td>3</td>
<td>Open label</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Zhu</td>
<td>34</td>
<td>Diet/Ex</td>
<td>12</td>
<td>Open label</td>
<td>+</td>
<td>N/A</td>
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<td>Suzuki</td>
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<td>12-24</td>
<td>Open label</td>
<td>+</td>
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<td>Harrison</td>
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<td>Orlistat</td>
<td></td>
<td>Open label</td>
<td>+</td>
<td>+</td>
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<td>Sabuncu</td>
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<td>Sibutramine/Orlistat</td>
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<td>Open label</td>
<td>N/A</td>
<td>+</td>
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<td>Luyckx</td>
<td>69</td>
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<td>27</td>
<td>Case series</td>
<td>+</td>
<td>+/-*</td>
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<td>Silverman</td>
<td>91</td>
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<td>Case series</td>
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<td>+</td>
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<td>Kral</td>
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<td>41</td>
<td>Case series</td>
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<td>+</td>
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<td>Dixon</td>
<td>36</td>
<td>Surgery</td>
<td>26</td>
<td>Case series</td>
<td>+</td>
<td>+</td>
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</tbody>
</table>
Weight Loss Works

31 Patients
Randomized, controlled trial
40% in intervention group lost 10% body weight vs 0% in control group
72% vs 30% achieved study endpoint

Weight loss of ≥ 7% associated with improvement in all parameters of NASH except fibrosis

Promrat K, Hepatology 2010;51:121-129
Non-alcoholic fatty liver disease
Weight loss works

- 36 patients with obesity underwent paired liver biopsies at time of laparoscopic gastric banding and 24 months later

- Mean weight loss 34 kg

- Histologic improvements in steatosis, inflammation, and fibrosis
  - Only 4 fulfilled criteria for NASH at second biopsy (24 at entry)
  - 18 had improvement in fibrosis by 2 stages

Liver Histology After Gastric Bypass

Hepatology 2004;39:1647-54
Significant Improvement in histology following bariatric surgery

1st biopsy

2nd biopsy at 8.5 months

Lifestyle Modification Program

- Assessed benefits of dietician led lifestyle modification for 12 months
  - Weekly meetings x 4 month, then monthly x 8
  - Moderate carbohydrate, low fat, low glycemic index
    - Emphasis on fruits and vegetables
  - Exercise: moderate intensity for 30 minutes 3-5 days/week
    - Increased to daily
- 154 Patients Enrolled
- Primary Endpoint
  - Remission of NAFLD: IHTG of < 5% by MRS
- 64% in intervention group resolved NAFLD
- 20% in control group resolved NAFLD

Wong VW, J Hepatol 2013
Degree of weight loss and resolution of NAFLD by hepatic TG content

Wong VW, J Hepatol 2013

% patients with resolution of NAFLD

<table>
<thead>
<tr>
<th>Percentage of weight loss from baseline to month 12</th>
<th>13</th>
<th>41</th>
<th>50</th>
<th>60</th>
<th>97</th>
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</thead>
<tbody>
<tr>
<td>&lt;3.0%</td>
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<tr>
<td>3.0-4.9%</td>
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<td>5.0-6.9%</td>
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<td>7.0-9.9%</td>
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<td></td>
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<tr>
<td>≥10.0%</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

n = 72  22  10  20  30

Wong VW, J Hepatol 2013
Low Glycemic Index Foods

• Beans
• Almonds
• Peanuts
• Walnuts
• Chickpea
• Small seeds
  – Sunflower
  – Flax
  – Pumpkin
• Whole intact grains
• Most vegetables
• Most sweet fruits (peaches, strawberries, mangos)
Exercise

• A recent large, cross-sectional study assessed the relationship between meeting/exceeding US national guidelines for physical activity and NAFLD severity
  – Self-reported
  – 813 patients
  – Divided into 3 exercise categories based on time spent in activity and metabolic equivalents (METS):
    • Inactive (54%)
    • Moderate (20%): >150 min/week; Activities with MET values 3-5.9
    • Vigorous (26%): >75 min/week: Activities with MET values >6

Kistler KD, Am J Gastroenterol 2011;106:460-468
Exercise

• Vigorous exercise associated with decreased adjusted odds of having NASH
  – OR: 0.65 (0.43-0.98)

• Doubling recommended time spent in vigorous exercise (>150 min/week), associated with decreased adjusted odds of advanced fibrosis
  – OR:0.53 (0.29-0.97)

Younger age, higher education, higher income, lower BMI and no diabetes

Kistler KD, Am J Gastroenterol 2011;106:460-468
Exercise

• Optimal Intensity
  – Goal is to maintain a lifestyle change
  – Moderate exercise, burning ~400 kcal/session
    – 3 times/week
    – Improves insulin resistance
    – Overall energy expenditure achieved per work-out more important than intensity
      » Training at 60% VO2max as effective as 80% VO2max
  – Weight loss
    – Need to work out for longer period of time

Ryan AS, Aging Health, 2010
Sleep

10 overweight adults assigned to sleep 8.5 vs 5.5 hours each night for 14 days

Moderate caloric restriction

Lost same amount of weight (~6.6 pounds)

Sleep curtailment decreased proportion of weight lost as fat by 55% and increased loss of fat-free mass by 60%

Nedeltcheva AV, Ann Intern Med 2010
### Treatment: Insulin Sensitizing Agents

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Drug</th>
<th>Duration (months)</th>
<th>Design</th>
<th>ALT</th>
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</table>
PIVENS Study Design

Randomization
Eligibility assessed by local pathologist
(1:1:1)
Wk 0

Vitamin E (r α-tocopherol) 800 IU/day

Placebo

Pioglitazone (30 mg/day)

Liver biopsy

Month -6

End of treatment
Liver Biopsy
Wk 96

Wk 0

Wk 96

Week 120 end of study

Sanyal et al., NEJM 2010
Pioglitazone and Vitamin E
PIVENS Trial

Summary of PIVENS findings

• Vitamin E effective over placebo for NASH
• Pioglitazone improved, IR, ALT, steatosis and inflammation, but not 1° outcome
• Only 34% (Pio) and 43% (Vit E) had histological response, neither improved fibrosis
• Cannot generalize to diabetics or cirrhotics
Why not empirically treat suspected NAFLD with vitamin E?

- 70-75% have NAFLD, most isolated steatosis
- 50% of patients don’t respond to Vitamin E
  – liver enzymes are not reliable to assess quiescence or progression
- The long-term safety remains unknown
- Prostate cancer risk? (absolute increase 1.6 per 1000 person yrs)
Metanalysis of Vitamin E – increased mortality?

- Different forms of Vitamin E
- Confounders not controlled for:
  - High dose Zn supplementation
  - Use of concomitant vitamin A
  - Smoking
- Trials not uniformly using Vit E as a treatment
- RCTs with no death excluded

*Annals of Int Med, 2005*
Pioglitazone for NASH

Pros

• Insulin sensitivity
• ALT
• Steatosis
• Inflammation
• ? Ballooning

Cons

• Weight gain (2–4.7 kg)
• Cardiac toxicity
• Fracture risk
• ? Bladder cancer

Meta-analysis of 19 trials (16,390 patients) with T2DM, pioglitazone

• Death, MI, or CVA: 4.4% of pioglitazone vs 5.7% of control (P = 0.005)
• More CHF in pioglitazone (2.3%) vs control (1.8%) (P = .002), no effect on mortality

Abbreviations: ALT, alanine aminotransferase; CHF, congestive heart failure; CVA, cerebrovascular accident; MI, myocardial infarction; NASH, nonalcoholic steatohepatitis; T2DM, type 2 diabetes mellitus.

Courtesy of Mary Rinella, MD.
Obeticholic acid

• Semi-synthetic bile acid derivative
• Farnesoid-X Receptor (FXR) agonist

Adorini L, Drug Dis Today 2012;17:988-997
Obetacholic Acid

- Triglyceride, fatty acid, and cholesterol synthesis
- Fatty acid oxidation
- Lipolysis

Liver
Common duct
Pancreas
Tail
Bile acid reabsorption
FGF15/19 production

Insulin secretion
Pancreatic duct
Intestine (duodenum)

Glucose uptake
Adipogenesis
Lipid storage

Insulin sensitivity

Skeletal muscle

Adipocytes
Glucose GLUT1

OCA-induced FXR activation

Drug Discovery Today
The FXR Ligand OCA in NASH Treatment (FLINT) Trial

**Design**
- Phase IIb, randomized, double-blind, placebo-controlled study to assess efficacy and safety of OCA 25 mg/d vs placebo in patients with NASH

**Duration**
- 72 weeks OCA 25 mg/d vs placebo

**Patients**
- 283 patients ≥18 years of age
  - Entry criteria
    - Histologic evidence of NASH based on a liver biopsy obtained ≤90 days prior to randomization
    - NAFLD Activity Score (NAS) ≥4

**Endpoints**
- **Primary**
  - Histologic improvement in NAS from baseline to Week 72
    - No worsening in fibrosis; and
    - Decrease in NAS of ≥2 points
- **Secondary**
  - Changes in fibrosis score, hepatocellular ballooning score, liver enzymes, hepatic fat fraction, insulin resistance/sensitivity, bile acid levels

Abbreviations: FXR, farnesoid X receptor; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; OCA, obeticholic acid.

FLINT: Effects of OCA on Histology

Primary endpoint: Improved histology
- NAS decrease of ≥2
- No increase in fibrosis

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<td>Patients meeting primary endpoint (%)</td>
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<td>21%</td>
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Abbreviations: NAS, nonalcoholic fatty liver disease activity score; OCA, obeticholic acid.
Treatment: Lipid Lowering Agents

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Statins are safe, improve ALT, not histology
Summary

- NAFLD is part of a systemic process and other diseases (cardiovascular) are associated
- More prevalent than previously estimated
  - Hispanics and diabetics at particular risk
- Biopsy is required, steatosis benign from hepatic point of view, NASH can progress to cirrhosis
- Smoking and excess alcohol are bad, but coffee and sleep likely good
Summary

- Weight loss goal of 10% is best for histopathology improvement.
- Moderate exercise may not be enough to effect change in NASH. Vigorous exercise for >150 min/week ideal.
- Vitamin E may be considered for patients with biopsy proven NASH with caveats (non-diabetic NASH).
- Pioglitazone can be used in NASH (non-diabetic NASH).
- Omega 3 fatty acids should also be considered. Not due to good data in NASH necessarily, but for cardiovascular benefit.
- Statins are safe.
Acknowledgements

• Paul Kwo

• Stephen Harrison