Nonalcoholic Fatty Liver Disease: Where Do We Stand In 2016

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Objectives-Non-Alcoholic Fatty Liver Disease

• Causes, Epidemiology, and Natural History of Non-alcoholic Fatty Liver Disease
• Pathogenesis and Clinical Presentation
• Treatment
Case

• 48 y/o Hispanic male referred for fatty liver on CT scan
• No alcohol history
• Past medical history
  – HTN, Hyperlipidemia, Obesity (BMI: 32), DM
• Meds:
  – Zocor, lisinopril, ASA, HCTZ, metformin
Case

- Labs
  - ALT: 67
  - AST: 58
  - Alk Phos: 140
  - Albumin: 3.9
  - HBV, HCV negative
  - Transferrin sat: 20%, ferritin: 400
  - HbA1C: 6.7
  - ANA: 1:320
  - Fasting Insulin: 25uIU/mL
Prevalence of Chronic Liver Disorders in the United States

NAFLD

• Spectrum of conditions characterized histologically mainly by macrovesicular steatosis and in the absence of consumption of alcohol in amounts thought to be harmful

• Two histological patterns
  - Steatosis alone
  - Steatohepatitis
Causes of Steatosis and Steatohepatitis

- "Primary"
- "Secondary"
  - Nutritional
  - Drugs
  - Inborn errors
  - Miscellaneous
Secondary Causes of Steatosis and Steatohepatitis

• **Nutritional**
  – Starvation
  – TPN
  – Rapid weight loss

• **Drugs**
  – Steroids
  – Oestrogens
  – *Tetracycline
  – *Valproate
  – *Anti retrovirals
  – § amiodarone

• **Metabolic**
  – Acute fatty liver of Pregnancy
  – Lipodystrophy
  – Weber-Christian Dz

• **Misc**
  – Small Bowel Overgrowth
  – Mushrooms

* mitochondrial defect
§ phospholipidosis
How much alcohol is too much for NASH?

• Alcoholic liver dz (conventional wisdom)
  – 30-40gm/day ♂ (3-4 drinks)
  – 60-80gm/day ♂ (6-8 drinks)

• Exclusion criteria for NASH Clinical Research Network:
  – 7 drinks (70g)/week ♂ or 1 drink/day
  – 14 drinks (140g)/week ♂ or 2 drinks/day
Epidemiology
NAFLD and NASH Prevalence

Prevalence (%)

- NAFLD-Overall: 46
- NAFLD-Hispanic: 58.3
- NAFLD-Caucasian: 44.4
- NAFLD-African American: 35.1
- NASH-Overall: 12.2
- NASH-Among Diagnosed NAFLD: 29.9

Williams CD et al, Gastroenterology 2011;140:124-31
NASH Prevalence Among Ethnic Groups

<table>
<thead>
<tr>
<th>Ethnic Group</th>
<th>Prevalence (%)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>12.2</td>
<td>40/328</td>
</tr>
<tr>
<td>Hispanic</td>
<td>19.4</td>
<td>14/72</td>
</tr>
<tr>
<td>Caucasian</td>
<td>9.8</td>
<td>20/205</td>
</tr>
<tr>
<td>African American</td>
<td>13.5</td>
<td>5/37</td>
</tr>
<tr>
<td>Other</td>
<td>6.7</td>
<td>1/14</td>
</tr>
</tbody>
</table>

p = 0.03

Williams CD et al, Gastroenterology 2011;140:124-31
NASH Prevalence Comparing Diabetics to Non-Diabetics

Williams CD et al, Gastroenterology 2011;140:124-31
Non-obese Population in a Developing Country Has a High Prevalence of NAFLD

- Prospective epidemiological study in West Bengal, India
- Diagnosis of NAFLD was by US + CT

Total N = 1,911

8.7% NAFLD

NAFLD

- Cardiovascular Disease
- OSA
- Hypothyroidism
- Diabetes
- ??Adenomatous Polyps
- Malignancy
Natural history of NAFLD
Natural History of NAFLD & NASH

NAFLD

-> Isolated fatty liver
  1. None to very minimal progression to cirrhosis
  2. No increased risk of death compared with the general population

NAFLD

NASH

-> NASH Cirrhosis
  1. Increased risk of death compared with general population. Causes of death, in order:
   a. Cardiovascular
   b. Malignancy
   c. Liver-related
  2. NASH with fibrosis portends worse prognosis
   a. Fibrosis progression associated with DM, severe IR, BMI, weight gain >5kg, rising ALT, AST, cigarette smoking

-> HCC
  ~7% over 6.5 years

-> Decompensation
  ~31% over 8 years

Pathogenesis and Diagnosis
Working Hypothesis: Metabolic Syndrome

Type II Diabetes
Fasting Glucose
≥ 110 mg/dL

Triglycerides
≥ 150 mg/dL

Obesity
Wax circumference
> 102 cm in men and > 88 cm in women

HDL Cholesterol
< 40 mg/dL (Men)
< 50 mg/dL (Women)

Systolic BP ≥ 130 mm Hg
or diastolic ≥ 85 mm Hg

The Adult Treatment Panel III clinical definition of the metabolic syndrome
Abdominal Adiposity: The Critical Adipose Depot
Pathogenesis of NASH

Insulin resistance

FFA + insulin + cytokines

Steatosis + metabolic dysregulation

ER stress

Oxidative stress

Mitochondrial injury

Inflammatory signaling

Apoptosis

Cell death

Stellate cell activation

fibrosis
NAFLD: Genetic Risk Factor

- PNPLA3 (Adiponutrin)
- Palatin-like phospholipase domain containing protein 3
- Rs738409[G] encoded for I148M
  - Associated with increased hepatic fat levels \((p=5.9 \times 10^{-10})\)
    - 2-fold increase in homozygotes
  - Associated with hepatic inflammation \((p=3.7 \times 10^{-4})\)
    - Associations remained significant after adjustment for obesity, DM, alcohol and ancestry
- Rs6006460[T], encoding S453I, is associated with lower hepatic fat
- 2 PNPLA3 variants account for 72% of ethnically related variation

The polymorphisms C-482T and T-455C in *APOC3* are associated with NAFLD and insulin resistance in Asian Indian Men

NAFLD subtypes

**NAFL** (non-alcoholic fatty liver)
- simple steatosis

**NASH** (non-alcoholic steatohepatitis)
- ballooned hepatocyte
- Fibrosis F0-F4 (cirrhosis)

AASLD Practice Guidelines 2012
Images adapted from Wikipedia.org; pathology.med.umich.edu; www.justintimemedicine.com
## Screening using Non-invasive Biomakers

<table>
<thead>
<tr>
<th>FibroTest</th>
<th>SteatoTest</th>
<th>NashTest</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\alpha)-Macroglobulin</td>
<td>(\alpha)-Macroglobulin</td>
<td>(\alpha)-Macroglobulin</td>
</tr>
<tr>
<td>Apolipoprotein A1</td>
<td>Apolipoprotein A1</td>
<td>Apolipoprotein A1</td>
</tr>
<tr>
<td>Haptoglobin</td>
<td>Haptoglobin</td>
<td>Haptoglobin</td>
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<tr>
<td>Total Bilirubin</td>
<td>Total Bilirubin</td>
<td>Total Bilirubin</td>
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<tr>
<td>GGT</td>
<td>GGT</td>
<td>GGT</td>
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<tr>
<td><strong>ActiTest</strong></td>
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</tr>
<tr>
<td>(\alpha)-Macroglobulin</td>
<td></td>
<td>(\alpha)-Macroglobulin</td>
</tr>
<tr>
<td>Apolipoprotein A1</td>
<td></td>
<td>Apolipoprotein A1</td>
</tr>
<tr>
<td>Haptoglobin</td>
<td></td>
<td>Haptoglobin</td>
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<tr>
<td>Total Bilirubin</td>
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<td>Total Bilirubin</td>
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<tr>
<td>GGT</td>
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<td>GGT</td>
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<tr>
<td>ALT</td>
<td></td>
<td>ALT</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td>BMI</td>
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<tr>
<td>Triglycerides</td>
<td></td>
<td>Triglycerides</td>
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<tr>
<td>Cholesterol</td>
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<td>Cholesterol</td>
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<tr>
<td>Weight</td>
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<td>Weight</td>
</tr>
<tr>
<td>Height</td>
<td></td>
<td>Height</td>
</tr>
<tr>
<td>AST</td>
<td></td>
<td>AST</td>
</tr>
<tr>
<td>Glucose</td>
<td></td>
<td>Glucose</td>
</tr>
</tbody>
</table>
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
Problems With Transient Elastography

• Anatomical barriers
  – Fat
  – Ascites
• Operator experience
• Conditions that influence liver stiffness
  – Acute hepatitis or hepatitis flare
  – Steatosis
  – Extra- and intrahepatic cholestasis
  – Cardiac failure
Red Flags for NASH

- Age
- Gender
- Hispanic
- HTN
- Obesity
- Diabetes
- ALT and AST level
- AST/ALT ratio
- Ferritin
- Insulin level

No lab test or imaging study will be able to predict with 100% accuracy

The more risk factors... the more concerned

Risk factors/Red Flags for NASH:
- Age ≥ 50
- Hispanic
- Ferritin > 1.5x normal (>300 women, >400 ng/ml men)
- BMI ≥ 30
- Diabetic
- AST/ALT>0.8
Cytokeratine-18 Fragments

For every 50 U/L increase in plasma K-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>
</tr>
</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>

Treatment
Lifestyle Modification

- Diet
- Exercise
- Sleep
- Coffee
- Vitamin D
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

Wong VW, J Hepatol 2013
Exercise

• Meta-analysis of 12 studies involving 439 patients with NAFLD
• Exercise included either aerobic and/or progressive resistance training
• Exercise frequency was from 2-6 days/week
  – Walking, cycling
  – Weight machines
• Pooled data in exercise alone groups showed significant improvement in steatosis (p=0.02)
• In 4/6 studies evaluating exercise alone, improvement seen without weight loss

Keating SE, J Hepatol 2012
AASLD Guidelines on Treatment (Weight Loss and Exercise)

• Weight loss generally reduces hepatic steatosis, achieved either by hypocaloric diet alone or in conjunction with increased physical activity.

• Loss of at least 3 – 5 % of body weight appears necessary to improve steatosis, but a greater weight loss (up to 10 % ) may be needed to improve necroinflammation.

• Exercise alone in adults with NAFLD may reduce hepatic steatosis but its ability to improve other aspects of liver histology remains unknown.

## Coffee and NASH

**Stage of Fibrosis**

<table>
<thead>
<tr>
<th>Coffee Caffeine Per Day (mg)</th>
<th>Stage of Fibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>255.89 (coffee cup equiv=1.87)</td>
<td>1 - negative ultrasound</td>
</tr>
<tr>
<td>170.30 (coffee cup equiv=1.24)</td>
<td>2 - bland steatosis</td>
</tr>
<tr>
<td>122.00 (coffee cup equiv=0.89)</td>
<td>3 - NASH stage 0-1</td>
</tr>
<tr>
<td>252.7 (coffee cup equiv=1.24)</td>
<td>4 - NASH stage 2-4</td>
</tr>
</tbody>
</table>

Treatment Options for NAFLD/NASH

- Weight Loss
- Exercise
- Omega 3 Fatty Acids—Premature to recommend
- Pioglitazone
- Vitamin E
- Metformin
- Atorvastatin—Premature to recommend
- Ursodiol—Not recommended
- Fore-gut bariatric surgery—not recommended to treat NASH alone
Pioglitazone and Vitamin E
PIVENS Trial

247 non-diabetic NASH pts

Vitamin E 800 IU day

Placebo

Pioglitazone 30mg day

48 weeks of treatment

Liver Bx

The primary outcome was an improvement in histologic findings, which required improvement by 1 or more points in the hepatocellular ballooning score; no increase in the fibrosis score; and either a decrease in the activity score for nonalcoholic fatty liver disease to a score of 3 points or less or a decrease in the activity score of at least 2 points, with at least a 1-point decrease in either the lobular inflammation or steatosis score.

The primary outcome was an improvement in histologic findings, which required improvement by 1 or more points in the hepatocellular ballooning score; no increase in the fibrosis score; and either a decrease in the activity score for nonalcoholic fatty liver disease to a score of 3 points or less or a decrease in the activity score of at least 2 points, with at least a 1-point decrease in either the lobular inflammation or steatosis score.

Changes from Baseline in ALT and AST

Changes in Insulin Resistance and Weight

AASLD Guidelines on Treatment

• Metformin has no significant effect on liver histology and is not recommended as a specific treatment for liver disease in adults with NASH.

• Pioglitazone can be used to treat steatohepatitis in patients with biopsy-proven NASH. However, it should be noted that the majority of the patients who participated in clinical trials that investigated pioglitazone for NASH were non-diabetic and that long-term safety and efficacy of pioglitazone in patients with NASH is not established.

• Vitamin E (α-tocopherol) administered at daily dose of 800 IU/day improves liver histology in non-diabetic adults with biopsy-proven NASH and therefore it should be considered as a first-line pharmacotherapy for this patient population.

• Until further data supporting its effectiveness become available, vitamin E is not recommended to treat NASH in diabetic patients, NAFLD without liver biopsy, NASH cirrhosis, or cryptogenic cirrhosis.

Looking ahead: Investigational agents

**FXR agonists** (eg. obeticholic acid)
- Phase 2: DM NAFLD and in NASH (FLINT trial)
- Phase 3 in NASH ongoing
- Insulin resistance data mixed
- Improved liver histology
- Worsening LDL
- Pruritus

<table>
<thead>
<tr>
<th>Agent</th>
<th>Trial completion dates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liraglutide (GLP-1 analogue)</td>
<td>Sept. 2013</td>
</tr>
<tr>
<td>Sitagliptin (DPP-4 inhibitor)</td>
<td>Nov. 2013</td>
</tr>
<tr>
<td>GFT505 (PPAR α/δ agonist)</td>
<td>Jan. 2015</td>
</tr>
<tr>
<td>Obeticholic Acid (Farnesoid X Receptor Ligand)</td>
<td>Jan. 2015</td>
</tr>
<tr>
<td>Metreleptin (recombinant human leptin)</td>
<td>Sept. 2015</td>
</tr>
</tbody>
</table>

### Statins and the Liver

<table>
<thead>
<tr>
<th></th>
<th>Normal ALT(1) N=1437</th>
<th>Abn ALT *(2) N=342</th>
<th>Liver dz(3) N=2245</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>57 + 12</td>
<td>54 + 12</td>
<td>48 + 18</td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td>201 + 51</td>
<td>205 + 53</td>
<td>196 + 60</td>
</tr>
<tr>
<td><strong>Base AST</strong></td>
<td>22 + 7</td>
<td>55 + 37</td>
<td>57 + 49</td>
</tr>
<tr>
<td><strong>Base ALT</strong></td>
<td>20 + 8</td>
<td>43 + 23</td>
<td>61 + 47</td>
</tr>
<tr>
<td><strong>Chol (mg/dl)</strong></td>
<td>245 + 44</td>
<td>240 + 82</td>
<td>213 + 51</td>
</tr>
<tr>
<td><strong>Atorvastatin</strong></td>
<td>47%</td>
<td>43%</td>
<td></td>
</tr>
<tr>
<td><strong>Simvastatin</strong></td>
<td>50%</td>
<td>55%</td>
<td></td>
</tr>
<tr>
<td><strong>Fluvastatin</strong></td>
<td>3%</td>
<td>2%</td>
<td></td>
</tr>
</tbody>
</table>

- Alcohol, HCV, HBV excluded
- Cohorts 1 and 2-hyperlipidemic patients
- Cohort 3 – no statins used

(Chalasani et al. Gastroenterology 2004)
## Statins and the Liver

### Table

<table>
<thead>
<tr>
<th></th>
<th>Normal ALT(1)</th>
<th>Abn. ALT(2)</th>
<th>Liver dz(3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statin duration (yr)</td>
<td>0.48±0.08</td>
<td>0.48±0.08</td>
<td></td>
</tr>
<tr>
<td>Statin discontinue</td>
<td>10.7%</td>
<td>11.1%</td>
<td></td>
</tr>
<tr>
<td>↑ AST/ALT 1-10 xULN</td>
<td>1.7%</td>
<td>4.7%</td>
<td>6.4%</td>
</tr>
<tr>
<td>p=0.002</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>↑ AST/ALT &gt;10 xULN</td>
<td>0.2%</td>
<td>0.6%</td>
<td>0.4%</td>
</tr>
<tr>
<td>p=0.6</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Alcohol, HCV, HBV excluded
- Cohorts 1 and 2 - hyperlipidemic patients
- Cohort 3 - no statins used

(Chalasani et al. Gastroenterology 2004)
NAFLD Diagnosis & Treatment Algorithm

If ≥ 2 red flags, consider liver biopsy initially

Likely NAFLD

Risk factors/Red Flags for NASH:
- Age ≥ 50
- Ferritin > 1.5x normal (>300 women, >400 ng/ml men)
- BMI ≥ 30
- Hispanic
- Diabetic
- AST/ALT>0.8

↑ ALT or Fatty Liver on Imaging

Rule out other chronic liver disease (ie. Viral hepatitis, autoimmune hepatitis, hemochromatosis, alcohol)

Check Vitamin D level & replaced if deficient

If < 1 red flag, optimize metabolic status & follow-up in 6 months

If ≥ 2 red flags, consider liver biopsy initially

NASH on liver biopsy

Diabetic or ≥ Stage 2
- 1-2 cups daily coffee
- Diet/Exercise*
- Consider:
  - Pioglitazone
  - Bariatric surgery IF comorbidities
  - Clinical trials

Nondiabetic & ≥ Stage 2
- 1-2 cups daily coffee
- Diet/Exercise*
- Consider:
  - Vitamin E
  - Bariatric surgery IF comorbidities
  - Clinical trials

Nondiabetic & < Stage 2
- 1-2 cups daily coffee
- Diet/Exercise*
- Consider:
  - Vitamin E
  - Clinical trials

No NASH on liver biopsy

Nondiabetic & < Stage 2
- 1-2 cups daily coffee
- Diet/Exercise*
- Consider:
  - Vitamin E
  - Clinical trials

No increased Liver related mortality
- Manage metabolic risk factors to minimize cardiovascular risks

Courtesy of Stephen Harrison M.D