Update on Fatty Liver Disease

40th Annual Advances in Internal Medicine
Bilal Hameed, MD

Learning Objectives

• Understand the pathogenesis of Non-Alcoholic Fatty Liver Disease (NAFLD)
• Identify patients with NAFLD
• Manage patients with NAFLD

Outline

• Pathogenesis
• Epidemiology
• Natural history
• Treatment
  ➢ Insulin sensitizers
  ➢ PIVENS

Nonalcoholic Fatty Liver Disease (NAFLD)

NAS (NAFL) 

Fat 

Inflammatory cells 

Ballooned liver cells 

± Fibrosis 

Risk of HCC

NASH 

Fat 

Cirrhosis 

Inflammation 

± Fat 

Risk of HCC
Obesity

What is NAFLD/NASH?
How does it happen?
Why is it important?

Foie Gras de Canard
NAFLD

History & Terminology

• 1980: “Nonalcoholic steatohepatitis (NASH) ...a hitherto unnamed disease” Ludwig et al. 1980

• A clinicopathologic condition
  - Usually seen in a population of obese, type II diabetics
  - Hepatic histology consistent with alcoholic hepatitis
  - Absence of significant alcohol use

NAFLD Terminology

• NAS (NAFL) - Nonalcoholic Steatosis
  - Simple fat (steatosis) - no inflammation, necrosis or fibrosis
  - Largely benign

• NASH - Nonalcoholic Steatohepatitis
  - Steatosis and ‘injury’ (ballooning, inflammation, fibrosis)
  - A potentially serious liver disease

• NAFLD - Nonalcoholic Fatty Liver Disease
  - An inclusive term for all of the above

Causes of Fatty Liver

Metabolic Syndrome
- Abdominal Obesity
- IGT/Diabetes
- Dyslipidemia
- Hypertension

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
Fat Accumulation in the Liver

- Increased fatty acid influx from adipose tissue:
  - Insulin resistance
  - Obesity
  - Diet

- Decreased fatty acid oxidation:
  - Hyperinsulinemia
  - Genetic
  - Leptin deficiency/resistance
  - Drugs

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

- Decreased VLDL assembly/secrection:
  - Insulin resistance
  - Genetic
  - Drugs

Triglyceride

Pathogenesis of NAFLD/NASH
The “Two Hit” Hypothesis

1st “Hit”
- Insulin resistance (Hyperinsulinemia)
- Leptin resistance
- ↑ FFA flux
- ↓ FFA oxidation
- ↓ Triglyceride export

2nd “Hit”
- Oxidative stress
- ↑ Lipid peroxidation
- ↑ Cytokines
- ↑ TNFα (Endotoxin)
- ↑ TGFβ
- ↑ Leptin

Normal → Steatosis → Inflammation & Fibrosis

Pathogenesis of NAFLD
Environment and Genetics

Nutrition; Activity

Genes

NAFLD

Why is NAFLD Important?

A complex, acquired metabolic disorder with a significant polygenic basis
Natural History

- **NAFLD**
  - Majority: Stable
  - 9-40%

- **NASH**
  - 4-13%
  - NASH/Cryptogenic Cirrhosis
  - Progression of Fibrosis
  - 9-20%
  - 40-60%
  - 5-7 yrs

- Cirrhosis related complications including HCC
  - 25-30%
  - 5-6 yrs

Prevalence: General Population

- **Prevalence**
  - General Population
  - 5-6 yrs

Prevalence

- **Prevalence of Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis Among a Largely Middle-Aged Population Utilizing Ultrasound and Liver Biopsy: A Prospective Study**
  - 400 enrolled
  - 144 underwent liver biopsy
  - 106 NAFLD, 35 NASH
  - 5 abnormal, 22 refused biopsy

Gastroenterology Jan, 2011

Williams D et al. Gastroenterology 2011
**Impact**

- About 2.7% of patients had evidence of advanced (stage 2-4 fibrosis) NASH.
- This suggests that 2 million middle-aged US adults may have advanced NASH.
- About 50% of the study population of asymptomatic middle-aged adults were found to have NAFLD.
NASH and Cryptogenic Cirrhosis

- NASH and cryptogenic cirrhosis share features of metabolic syndrome (Caldwell, 1999)
- NASH develops following liver transplantation in ~ 20% of patients with cryptogenic cirrhosis (Contos, 2001; Ong, 2001; Ayata 2002, Yalamanchili, 2010)

Distribution of NAFLD by Racial/Ethnic Group in Alameda County

Weston et al. Hepatology 2005

The “NAFLD Gene”

Romeo et al. Nature Genetics Sept 2008

- PNPLA3 - Patatin-like phospholipase family
- rs738409(G) (I141M) \( P = 5.9 \times 10^{-10} \) association with hepatic steatosis
  - Highest allele frequency in Hispanics
- rs600646(T) (S453I) - Associated with less hepatic steatosis in African Americans
Natural History of NAFLD

Adams et al. Gastroenterology 2005

- Reduced life expectancy vs. general population.
- Liver disease the third leading cause of death after cancer (1) and cardiovascular disease (2).

Natural History of NAFLD

Ong et al. J Hepatology 2008

- NHANES III
- Eligible: 12,822 (817 NAFLD)
- F/U: 8.7 yrs (median)
- Liver disease 3rd leading cause of death (CVS, malignancy) vs 11th in control population without NAFLD

The Heart of the Matter

Two Unfortunate Victims of the Metabolic Syndrome…?

Obesity
Insulin Resistance
Metabolic Syndrome

NAFLD
Hepatic Insulin Resistance, Inflammation

Cardiovascular Disease
Risk of CAD in NASH Cirrhosis

<table>
<thead>
<tr>
<th>Variables/Groups</th>
<th>NASH-related Cirrhosis</th>
<th>Cirrhosis Of Other Etiologies</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (n)</td>
<td>60</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>28/32</td>
<td>32/28</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>55.4±8.9</td>
<td>54.6±10.4</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>Smoking</td>
<td>17 (28.3%)</td>
<td>14 (23.3%)</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>Obesity (BMI&gt;30)</td>
<td>32 (53.3%)</td>
<td>4 (6.6%)</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Hypertension</td>
<td>32 (51.6%)</td>
<td>12 (20%)</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>29 (65%)</td>
<td>19 (31.6%)</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Metabolic Syndrome*</td>
<td>29 (48.3%)</td>
<td>6 (10%)</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>13 (21.6%)</td>
<td>2 (3.3%)</td>
<td>p&lt;0.05</td>
</tr>
</tbody>
</table>

Association of NAFLD with Coronary Artery Disease (CAD)

- Elective coronary angio (n=317)
- US same day
- 85 Normal or mild CAD
- 232 Clinically relevant CAD

Does NAFLD Increase Cardiovascular Morbidity?

- Elevated ALT predicts increased risk of cardiovascular events (Ioannou, 2006; Schindhelm, 2007)
- NAFLD independently associated with endothelial dysfunction, carotid atherosclerosis, coronary artery disease and increased risk of cardiovascular events (Targher, 2007; Mirbagheri, 2007; Hamaguchi, 2007, Kadayifci, 2008)

Table 1. Demographic, clinical and laboratory data for the two groups of patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A (n=85)</th>
<th>Group B (n=232)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean±SD)</td>
<td>51.3±4.5</td>
<td>59.6±10.2</td>
<td>0.003**</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>55:34</td>
<td>160:52</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.002**</td>
<td>2.94 (1.47-5.91)</td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>0.014*</td>
<td>2.31 (1.19-4.48)</td>
<td></td>
</tr>
<tr>
<td>HTN</td>
<td>0.109</td>
<td>1.63 (0.90-2.98)</td>
<td></td>
</tr>
<tr>
<td>LDL</td>
<td>0.109</td>
<td>0.99 (0.98-1.00)</td>
<td></td>
</tr>
</tbody>
</table>

*P < 0.05; **P < 0.01.
HTN, hypertension; LDL, low-density lipoproteins.
NAFLD Association with CAD

Implications

- The presence of NAFLD indicates a higher risk for cardiovascular disease
- Importance of screening for NAFLD in patients at risk
- Detection of NAFLD on ultrasound should alert clinicians to:
  - Coexistence of underlying CVD risk factors
  - Need for patient education
  - Need for assessment (screening) for coronary artery and carotid atherosclerosis

NAFLD/NASH

How do we diagnose it?

(And identify patients with, or at risk for, developing advanced liver disease?)

NAFLD

A Clinically Silent Disease

- Symptoms:
  - None 20 - 77%
  - Right upper quadrant pain 25 - 48%
  - Fatigue 50 - 75% (Obstructive sleep apnea in 40%)
- Signs:
  - Overweight/Obese 85 - 95%
  - Acanthosis nigricans 10 - 15%
  - Hepatomegaly 25 - 50%
- Laboratory:
  - ALT, AST - modest elevation
  - “Normal enzymes” (up to 80% of NAFLD?)

NASH

Laboratory Findings

- Mild elevation of ALT levels; levels typically are <1.5 the upper normal level
- ALT > AST (AST > ALT suggests significant fibrosis, cirrhosis). AST>>ALT suggests alcohol
- Alkaline phosphatase level elevation - uncommon
- Hyperglycemia (diabetes in one third of patients)
- Hyperlipidemia in 25 – 30%
NAFLD: Approach to Diagnosis
“Rule Out” Laboratory Tests

- Serology for hepatitis B and C (HBsAg, anti-HBc; anti-HCV)
- Hemochromatosis (iron, transferrin, ferritin, genetic testing [C282Y, H63D])
- Autoimmune liver diseases (AIH, PBC, PSC: SPEP, ANA, ASMA, AMA, ANCA, IgG, IgM)
- Wilson’s disease (ceruloplasmin, 24 h urine copper),
- α1-Antitrypsin deficiency (α1-AT)
- Muscle disease (CK)
- Celiac disease (TTG antibody)

NAFLD: Ultrasonography

Asymptomatic + ‘Marker Negative’ Liver Enzyme Elevation + Fatty Liver on US = 96% Positive Predictive Value for NAFLD

Joy & Scott, Eur J Gastroenterol Hepatol, 2003

NAFLD: CT Imaging

Normal Liver
Liver = Spleen

NAFLD
Liver < Spleen

To Biopsy or Not to Biopsy

RISK
BENEFIT
Complications of Liver Biopsy

<table>
<thead>
<tr>
<th>Complication</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>25</td>
</tr>
<tr>
<td>Hypotension</td>
<td></td>
</tr>
<tr>
<td>Pneumothorax</td>
<td></td>
</tr>
<tr>
<td>Hemoperitoneum</td>
<td>1 - 3.5</td>
</tr>
<tr>
<td>Hemobilia</td>
<td></td>
</tr>
<tr>
<td>Gallbladder perforation</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>0.01%</td>
</tr>
</tbody>
</table>


When to Consider a Liver Biopsy

- Predictors of advanced fibrosis
  - Age >45, diabetic, obese, AST/ALT > 1, ALT > 3-5x N
- Cannot exclude other types of liver disease (autoimmune hepatitis, drug-induced liver disease)
- Atypical phenotype: NAFLD in absence of obesity or metabolic syndrome
- Evidence of iron overload
- Confirm clinical suspicion of cirrhosis
  - Platelet count, imaging
- Support major therapeutic decision - bariatric surgery?

NAFLD

Histology of NASH

**GRADE**
- Steatosis (0 - 3)
- Inflammation (0 - 2)
- Liver cell injury (Ballooning) (0 - 2)

**STAGE**
- Fibrosis (0 - 4)

- NAFLD Activity Score (NAS) = unweighted sum of steatosis, lobular inflammation & ballooning scores.
- NAS =/> 5 correlates with diagnosis of NASH
- NAS <3 correlates with “not NASH”

NAFLD

Identifying Patients at Risk for Progressive Disease

Kleiner et al., 2005
Noninvasive Diagnosis of Progressive Disease

### Fibrosis
- Simple Test
  - Age
  - BMI
  - Hyperglycemia
  - Platelets
  - Albumin
  - AST>ALT
- ELF Panel
  - Hyaluronate
  - P3NP
  - TIMP1
- FibroTest®
  - Age
  - Sex
  - α2-Macroglobulin
  - Haptoglobin
  - GGT
  - Total Bilirubin
  - Apo A1
  - ALT
- The Future
  - Biomarkers for apoptosis & necrosis (CK-18)
  - Lipidomic signature
  - Genomic (SNP) profiling

Angulo 2007; Guha 2008; Ratziu 2006; Cales 2005; Puri 2009

### NASH

**NAFLD**
What to do about it?
Current management

NAFLD/MetS Management

- Obesity
  - Insulin Resistance
    - NAFLD
    - Antioxidants
    - Lipotropic agents
    - Cytoprotectants
- Diabetes
- Hypertension
- Hyperlipidemia
- Clinical Trials!

Diet
Exercise
Medication
Surgery

- Metformin
- TZDs
- AR,B
- Statin
- Fibrate

### Treatment Strategies for NAFLD
Optimal Treatment

- Improves the underlying MetS/Insulin resistance
- Prevents progressive liver fibrosis
- Improves cardiovascular risk
- High patient acceptability
- Durable
- Low rate of complications
**Risks from Prescription Drugs?**

**Statins**

- Comparison of hyperlipidemic patients with baseline liver enzyme elevation, with and without statin treatment
  - No difference in enzyme elevations on statin drugs between the cohorts followed for 6 months
- Small prospective cohort studies in NAFLD show improvement in liver enzymes with statins, benefit to portal pressure, ALT in HCV
- Statins are acceptably safe in NAFLD
- Monitor labs; D/C if ALT > 3x normal

_Henderson 2009; Nelson 2009; Browning 2006; Chalasani 2004; Kadayifci, 2003_

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**Treatment of NASH**

**Weight Reduction**

**NAFLD - Diet & Exercise**

- 10 published Studies (626 patients)
- Liver histology endpoint in only 4 studies (123 patients)
- Strong evidence for stabilization or reversal of histological fibrosis is lacking

_Bellantani et al, Hepatology 2008_

**Weight Loss**

- Effective
  - 9-10% body weight loss: improved insulin sensitivity, liver enzymes, visceral adiposity, steatosis and inflammation
- Sustainability??
  - Data analysis of 1310 patients who lost 10% body weight in 1999-2002 NHANES study
    - 66.5% maintained or reduced weight
    - Factors assoc with weight increase: Mexican-American and Sedentary lifestyle

Treatment of NAFLD

Weight Loss Drugs

<table>
<thead>
<tr>
<th>Study</th>
<th>Therapy</th>
<th>N</th>
<th>Study Type</th>
<th>Treatment Duration</th>
<th>Liver Enzyme Level</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harrison, 2002</td>
<td>Orlistat</td>
<td>10</td>
<td>Open label</td>
<td>24 mo</td>
<td>Improved</td>
<td>Improved (S,I,F)</td>
</tr>
<tr>
<td>Harrison, 2003</td>
<td>Orlistat</td>
<td>3</td>
<td>Case Series</td>
<td>6 – 12 mo</td>
<td>Improved</td>
<td>Improved (S,I,F)</td>
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<tr>
<td>Harrison, 2009</td>
<td>Orlistat vs Vit E</td>
<td>50</td>
<td>Randomized</td>
<td>36 weeks</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>Sabuncu, 2003</td>
<td>Sibutramine</td>
<td>25</td>
<td>Open label</td>
<td>6 mo</td>
<td>Improved AST, some had increased Alk Phos</td>
<td>ND</td>
</tr>
</tbody>
</table>

Bariatric Surgery & NASH

Mummadi R, et al. Effect of bariatric surgery on nonalcoholic fatty liver disease: systematic review and meta-analysis. CGH 2008

- Systematic review and meta-analysis (50% RYGB)
- 15 studies (1990-2007), 766 patients with pre-wt loss and follow up biopsies; 8 - 41 months. NAFLD in 83.2%; fibrosis in 65.2%

| Fat+Inflammation (Steatohepatitis) | 81.3% | (69.5%)* |
| Fibrosis | 65.5% |

* Complete resolution

Caveats
- Operative morbidity/mortality (0.05% for LAGB)
- Late technical complications
- Malnutrition
- Rapid weight loss
  - Enzyme increases
  - Worsening portal inflammation & fibrosis
  - Acute/subacute liver failure

Treatment of NASH

Drug Therapy
Controlled Trials in Patients with NAFLD

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Design</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Duration (Months)</th>
<th>Histologic Improvement</th>
<th>ALT Improvement</th>
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</thead>
<tbody>
<tr>
<td>Lavine (2001)</td>
<td>OL</td>
<td>Vitamin E</td>
<td>--</td>
<td>4—10</td>
<td>NA</td>
<td>+</td>
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<tr>
<td>Hasegawa et al. (2001)</td>
<td>OL</td>
<td>Vitamin E</td>
<td>--</td>
<td>12</td>
<td></td>
<td>+</td>
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<tr>
<td>Harrison et al. (2003)</td>
<td>RCT</td>
<td>Vitamin E and vitamin C</td>
<td>Placebo</td>
<td>6</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Sanyal et al. (2004)</td>
<td>RCT</td>
<td>Vitamin E + pioglitazone</td>
<td>Vitamin E</td>
<td>6</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Uygün et al. (2004)</td>
<td>RCT</td>
<td>Metformin</td>
<td>Diet</td>
<td>12</td>
<td>-</td>
<td>+</td>
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<tr>
<td>Bugianesi et al. (2005)</td>
<td>RCT</td>
<td>Metformin</td>
<td>Vitamin E or diet</td>
<td>12</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Bellfort et al. (2006)</td>
<td>RCT</td>
<td>Diet + pioglitazone</td>
<td>Diet + placebo</td>
<td>6</td>
<td>+</td>
<td>+</td>
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<td>Dufour et al. (2008)</td>
<td>RCT</td>
<td>Vitamin E + UDCA</td>
<td>UDCA + placebo</td>
<td>24</td>
<td>+</td>
<td>-</td>
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<td>Yakaryılmaz et al. (2007)</td>
<td>OL</td>
<td>Vitamin E</td>
<td>--</td>
<td>6</td>
<td>+</td>
<td>-</td>
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<tr>
<td>Riattu et al. (2008)</td>
<td>RCT</td>
<td>Rosiglitazone</td>
<td>Placebo</td>
<td>12</td>
<td>+</td>
<td>-</td>
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<tr>
<td>Alhaj et al. (2009)</td>
<td>RCT</td>
<td>Diet/exercise + pioglitazone</td>
<td>Diet/exercise + placebo</td>
<td>12</td>
<td>+</td>
<td>-</td>
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<tr>
<td>Nair and Gedik (2009)</td>
<td>RCT</td>
<td>Metformin</td>
<td>Lifestyle modification</td>
<td>6</td>
<td>NA</td>
<td>+</td>
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<td>Omar et al. (2010)</td>
<td>RCT</td>
<td>Metformin</td>
<td>Rosiglitazone or pioglitazone + metformin</td>
<td>12</td>
<td>+</td>
<td>NA</td>
</tr>
<tr>
<td>Sanyal et al. (2010)</td>
<td>RCT</td>
<td>Pioglitazone or vitamin E</td>
<td>Placebo</td>
<td>24</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Treatment of NASH
Metformin (Mostly Non-Diabetics)

<table>
<thead>
<tr>
<th>Study</th>
<th>Therapy</th>
<th>N</th>
<th>Study Type</th>
<th>Treatment Duration</th>
<th>Liver Enzyme Level</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coyle, 1999</td>
<td>Metformin</td>
<td>2</td>
<td>Open</td>
<td>4 – 11 mo</td>
<td>Improved</td>
<td>Improved</td>
</tr>
<tr>
<td>Marchesini, 2001</td>
<td>Metformin</td>
<td>20</td>
<td>Open</td>
<td>4 – 11 mo</td>
<td>Improved</td>
<td>ND</td>
</tr>
<tr>
<td>Uygün, 2004</td>
<td>Metformin vs Diet</td>
<td>36</td>
<td>Open, Rand.</td>
<td>6 mo</td>
<td>Improved</td>
<td>Improved, but no</td>
</tr>
<tr>
<td>Nair, 2004</td>
<td>Metformin</td>
<td>15</td>
<td>Open</td>
<td>12 mo</td>
<td>Not sustained</td>
<td>Variable</td>
</tr>
<tr>
<td>Schwimmer, 2005</td>
<td>Metformin</td>
<td>10 (peds)</td>
<td>Open</td>
<td>24 weeks</td>
<td>Improved</td>
<td>ND</td>
</tr>
<tr>
<td>Bugianesi, 2005</td>
<td>Metformin Vs vi E or Diet</td>
<td>110</td>
<td>Open, Rand.</td>
<td>12 mo</td>
<td>Improved</td>
<td>Improved (S, I, F)</td>
</tr>
<tr>
<td>Haukland 2008</td>
<td>Metformin Vs Placebo</td>
<td>49</td>
<td>Open, Rand.</td>
<td>6 mo</td>
<td>No difference</td>
<td>No difference</td>
</tr>
</tbody>
</table>

Treatment of NASH
Thiazolidinediones (TZDs)

- Improve insulin sensitivity
- Inhibit inflammatory signaling
- Inhibit fibrogenesis

RCTs of TZDs in NASH

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Type of study</th>
<th>Country</th>
<th>Duration, month</th>
<th>Dose, mg/day</th>
<th>Number of patients in treatment group (dropouts)</th>
<th>Number of patients in placebo group (dropouts)</th>
<th>Design</th>
<th>Blinding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sanyal et al. 2010</td>
<td>Multicentre</td>
<td>US</td>
<td>24</td>
<td>30</td>
<td>80 (14)</td>
<td>83 (12)</td>
<td>Randomised, placebo-controlled</td>
<td>Double-blind</td>
<td></td>
</tr>
<tr>
<td>Alhaj et al. 2008</td>
<td>Multicentre</td>
<td>UK</td>
<td>12</td>
<td>30</td>
<td>37 (6)</td>
<td>37 (7)</td>
<td>Randomised, placebo-controlled</td>
<td>Double-blind</td>
<td></td>
</tr>
<tr>
<td>Bellfort et al. 2006</td>
<td>Multicentre</td>
<td>US</td>
<td>6</td>
<td>45</td>
<td>26 (13)</td>
<td>21 (4)</td>
<td>Randomised, placebo-controlled</td>
<td>Double-blind</td>
<td></td>
</tr>
</tbody>
</table>

Aliment Pharmacol Ther 2011
**PIVENS** (Pioglitazone/Vit E/Placebo - Adults)
247 patients, 96 weeks

**TONIC** (Metformin/Vit E/Placebo - Pediatric)
173 patients, 96 weeks

Sanyal AJ & the NASH CRN. A Randomized Controlled Trial of Pioglitazone or Vitamin E for Nonalcoholic Steatohepatitis. Presented, 60th Annual AASLD Meeting, Boston, November 2, 2009.

*Decrease in NAS by ≥ 2 pts with ≥ 1 pt decrease in ballooning.*
PIVENS
Change in ALT and AST

PIVENS
Conclusions

- Vitamin E superior to placebo for treatment of NASH in adult, non-diabetics
- Pioglitazone
  - Did not meet the prespecified level of significance for the primary endpoint
  - Resulted in weight gain
  - Superior to placebo in improving other key histological features and liver enzymes.
- Neither drug improved fibrosis score over the duration of the study


Caution About Vitamin E?

- Inhibit platelet aggregation & antagonizes vitamin K-dependent clotting factors (Animal studies)
- Increase risk of heart failure in patient with DM and vascular disease (Lonn E et al. JAMA March,2005)
- Vit E increased the risk for haemorrhagic stroke (Shurks et al. BMJ November, 2010)
- Increase risk of prostate cancer

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=.008
Vitamin E

- Vit E at 800 IU/day leads to histological improvement in NASH in ~50% of patients
- Vit E is the current treatment of choice for biopsy proven NASH (non diabetics)
  -- Duration? Safety
  -- Predictors of response
- Need for other agents and clinical trials

It’s Not Any Old Vitamin E!

- Nature Made® (Pharmavite®) Brand
- RRR-α-Tocopherol
- Marketed as Vitamin E Natural (d-Alpha Tocopherol)
- 800 IU or 400 IU
- This is NOT dl-Alpha Vitamin E (synthetic Vitamin E)
- This does not imply that all other natural vitamin E analogues (8 in all) would not be as, or even more, effective

Pharmacological Treatment of NASH - What Lies Ahead

- Determinants of Vit E responsiveness
- Combination therapies aimed at improving insulin resistance and oxidative stress
- FLINT Trial (Obeticholic acid [INT 747] FXR agonist) - NASH CRN
- GLP-1 receptor agonists
- Omega-3 PUFA
- Comparison of drug therapies with bariatric surgery on histological NASH
- Identification and validation of noninvasive diagnostic & treatment response variables

NAFLD

When to obtain a GI opinion/referral?

- Need for liver biopsy
- Atypical liver enzyme pattern (e.g., cholestatic)
- Atypical patient (non-obese, no MetS risk factors)
- Possibility of participation in clinical trials
- Suspicion of cirrhosis (spiders, platelets, splenomegaly, ultrasound findings)
NASH: Current Standard of Therapy

• First line:
  – Lifestyle modification - weight loss through diet and exercise - effective, but high probability of failure
  – Drug therapy of MetS complications - dyslipidemia, hypertension, diabetes

• Second line: Vitamin E and Clinical trial enrollment - “work in progress”

• Third line: Patient identified at risk for progressive disease: bariatric procedure

• Last line: Empiric Rx: antioxidants, pentoxifyline, ursodiol, betaine - worthwhile?

Thank You

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