Nonalcoholic Fatty Liver Disease (NAFLD) Turns 38-What Have We Learned?

Jay D. Horton, M.D.

This is to acknowledge that Jay D. Horton, M.D. has disclosed financial interests or relationships with commercial concerns directly or indirectly related to this program. Dr. Horton will be discussing off-label uses in his presentation.
**Presenter:** Jay D. Horton, M.D.

**Rank:** Professor

**Division:** Digestive and Liver Diseases

**Purpose & Overview:**
To discuss and explain the underlying mechanisms responsible for the development of nonalcoholic fatty liver disease as well as the mechanism of action for new drugs under development for the treatment of nonalcoholic fatty liver disease.

**Objectives:**
1. Understand the underlying changes in fatty acid metabolism that result in fat accumulation in liver.
2. Understand the genetic contributions to NAFLD.
3. Understand the risk factors associated with the development of NAFLD.

**Biosketch:**
Dr. Jay D. Horton is the Director of the Center for Human Nutrition and Professor of Internal Medicine and Molecular Genetics. He obtained his B.S. and M.D. degrees from the University of Iowa and completed his Internal Medicine residency, gastroenterology fellowship, and Howard Hughes post-doctoral fellowship at UT Southwestern. Dr. Horton’s research interests are in determining how regulators of fat metabolism contribute to the development of fatty liver and delineating the function of PCSK9, a protein secreted into the blood that regulates LDL receptors in liver.
Facts Regarding NAFLD

- Approximately **83 million** people in the U.S. have NAFLD-projected to increase to **101 million** by 2030 (1).
- Global prevalence of NAFLD is ~25% (2).
- Insulin resistance is the key underlying metabolic abnormality present in the majority of individuals who develop of NAFLD and NAFLD could be considered a component of the metabolic syndrome (3, 4).
- Patients with NAFLD are twice as likely to die of cardiovascular disease than from liver disease (5).
- The clinical disease progression of NAFLD is highly variable but those with NASH progress to fibrosis ~ 2X faster than those with only steatosis on initial biopsy (1).
- NAFLD can lead to the development of hepatocellular carcinoma (HCC) even in the absence of cirrhosis and NAFLD-associated HCC represents 18% of those listed for transplant (1, 6).
- Current treatment options for NASH per 2018 AASLD Practice Guidelines (7):
  1) **Weight loss**
     At least 3%-5% of body weight appears necessary to improve steatosis, but a greater weight loss (7%-10%) is needed to improve the majority of the histopathological features of NASH. Foregut bariatric surgery can be considered in otherwise eligible obese individuals with NAFLD or NASH. It is premature to consider foregut bariatric surgery as an established option to specifically treat NASH.
  2) **Vitamin E**
     Daily dose of 800 IU/day improves liver histology in nondiabetic adults with biopsy-proven NASH and therefore may be considered for this patient population. Vitamin E is not recommended to treat NASH in diabetic patients, NAFLD without liver biopsy, NASH cirrhosis, or cryptogenic cirrhosis.
  3) **Pioglitazone**
     Dose of 30 mg/day improves liver histology in patients with and without T2DM with biopsy-proven NASH. Therefore, it may be used to treat these patients. Risks and benefits should be discussed with each patient before starting therapy. Should not be used to treat NAFLD without biopsy-proven NASH.
References


Case Presentation

• 49 y/o Hispanic female with Type 2 DM and HTN presents for evaluation of abnormal LFTs found in health screen
• PE significant for BMI of 42
• Labs: ALT 80, AST 40, Pts 300, INR 0.5
• Hep. serologies neg, ANA, AMA, AMSA, Ferritin, \( \alpha \)-1 antitrypsin all NL
• Abdominal Sono: Increased echogenicity

Definitions

• Nonalcoholic Fatty Liver Disease (NAFLD)
  – Clinicopathologic syndrome that ranges from fatty liver alone to fatty liver plus inflammation/fibrosis
• Hepatic Steatosis
  – Excessive lipid accumulation in hepatocytes
• Nonalcoholic Steatohepatitis (NASH)
  – Severe form of NAFLD
  – Includes hepatic steatosis plus hepatitis

Liver Histology of NAFLD

- Normal Liver
- Ballooning Degeneration
- Steatosis
- NASH
Diagnosis of NAFLD

• Exclude other causes:
  – serologic tests for viral hepatitis
  – iron studies
  – ceruloplasmin
  – α-1 antitrypsin
  – anti-mitochondrial & antinuclear Ab
• Mild-moderate (2-5 X) increase in ALT/AST
• Radiologic studies very suggestive
  – Ultrasound, Unenhanced CT, MRI, MRS
• Liver biopsy

Abnormal ALT in Hepatic Steatosis

Hepatic Triglyceride Content (HTGC) in Subjects with No Risk Factors

Distribution of Hepatic Fat in DHS

Median: 3.6%

Prevalence of Hepatic Steatosis

African Americans:
- 5.5%

European Americans:
- 4.5%

Hispanics:
- 5.0%


Estimated Prevalence of NAFLD in the U.S.

Normal

Simple Steatosis

Steatohepatitis

Cirrhosis

Obesity Insulin Resistance

~33%

~20%

~15%

103 million

20.7 million

3.1 million


BMI and Insulin Resistance is Correlated with Hepatic Steatosis in the DHS

Progression of NAFLD

- n=103
- Mean Biopsy Interval = 3.2 yrs
- Range = 0.7-21 yrs

Clinical Outcomes


Metabolic Alterations that Lead to Hepatic Steatosis

- Cohen et al. Science 2011; 332:1519-1523
Adipose Fatty Acid Release:
Increased FFA from Adipose (~60%)

Fatty Acid Synthesis:
Increased in NAFLD (~25%)

VLDL-TG Secretion:
Increased in Most NAFLD Subjects
Exomewide Scan for SNPs Associated with Liver Fat in DHS


**TM6SF2 Variant Associated with NAFLD**

- Frequency of *TM6SF2* p.Glu167Lys: 7.2% in Europeans, 3.4% in African Americans, and 4.7% in Hispanics
- Carriers of *TM6SF2* variant had elevated mean and median liver TGs, higher ALTs, lower plasma TGs & LDL

**Metabolic Alterations that Lead to Hepatic Steatosis:**

*Reduced Secretion (4-7%) with TM6SF2 SNP*
Hepatic β-oxidation:
Increased in NAFLD


Metabolic Alterations that Lead to Hepatic Steatosis

Cohen et al. Science 2011;332:1519-1523

Genetic Variants Associated with NAFLD

<table>
<thead>
<tr>
<th>Gene</th>
<th>Steatosis</th>
<th>NASH</th>
<th>OR</th>
<th>Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>PNPLA3</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>3.26</td>
</tr>
<tr>
<td>TM6SF2</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>1.65</td>
</tr>
<tr>
<td>MBOAT7</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>1.30</td>
</tr>
<tr>
<td>GCKR</td>
<td>+</td>
<td>-</td>
<td>?</td>
<td>1.45</td>
</tr>
<tr>
<td>HSD17β1*3</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GWAS of Hepatic TG Content in DHS
Nonsynonymous DNA Variations (n = 9,229)

PNPLA3


PNPLA3:I148M – Ethnic-specific Allele Frequencies in Dallas Heart Study

PNPLA3: I148M Allele Frequency

Prevalence of Hepatic Steatosis


PNPLA3 I148M is Associated with Disease Progression

Sokoloski et al. J Lipid Res. 2009
Tien C. et al. Nat Genet. 2010
Mueller et al. J. Hepatol. 2011
Trepo et al. J. Hepatol. 2011

↑ LFTs

NAFLD
Alcohol
MM: 3.8 X risk cirrhosis
**PNPLA3 Polymorphism Exacerbates Effect of Obesity on Hepatic TG Content**

![Graph showing the effect of PNPLA3 polymorphism on hepatic TG content in different BMI categories.](image1)

*P < 0.01
**P < 0.001

**Estimated Prevalence of NAFLD in the U.S.**

- Normal: ~33%
- Simple Steatosis: ~20%
- Steatohepatitis: ~15%
- Cirrhosis: ~20.7 million

**PNPLA3, TM6SF2, MBOAT7, HSD17B13**

- Obesity
- Insulin Resistance

**Cause of HCC for Waitlisted Transplant Candidates**

- **2002**: Hep C 53%, Hep B 14%, Other 33%
- **2017**: Hep C 48%, Hep B 14%, ALD 18%, NASH 14%

![Chart showing the change in cause of HCC from 2002 to 2017.](image2)
**Diagnosis and Management of NAFLD**

- **ETOH**
  - Ongoing or recent ETOH of >21 drinks/wk in male and >14 drinks/wk in females considered significant (Strength 2, Quality C)

- **Screening in Primary Care of High Risk Groups and Family Members**
  - Not recommended due to lack of treatment options and lack of evidence of long-term benefits and cost effectiveness (Strength 1, Evidence B)

**Steatosis on Imaging**

- No features of cirrhosis
  - CPRs or stiffness measurement
  - Persistent Abnl LFTs
  - Suggestive of fibrosis
  - Re-evaluate in 3-5 yrs

- Findings suggestive of cirrhosis
  - CPRs or stiffness measurement
  - Consistent with cirrhosis
  - Consider liver bx
  - Initiate HCC and variceal screening

**Therapeutic Trials for NAFLD**

- **Weight Loss (Strength 1, Evidence A)**
  - 8 RCTs (n=373)
  - >3-5% weight loss improved NAS
  - Improved HOMA, glucose tolerance, and plasma lipids
Therapeutic Trials for NAFLD

- **Vitamin E (Strength-1, Quality-B)**
  - 5 RCTs (n=685)
  - Improvement in steatosis and inflammation no progression of fibrosis
  - Should be considered first-line therapy (800 IU/d) in non-diabetics with biopsy-proven NASH
  - Not recommended in diabetics, NAFLD without liver biopsy, NASH cirrhosis, or cryptogenic cirrhosis

- **TZDs (Strength-1, Evidence-B)**
  - 11 RCTs (n=862)
  - Improved steatosis, ballooning and inflammation but not fibrosis
  - Improved HOMA, A1c, HDL, TGs but weight gain
  - Pioglitazone (30 mg/d) can be used for biopsy-proven NASH (most Pts nondiabetic and no long-term safety data)

- **Metformin (Strength-1, Evidence-A)**
  - 11 RCTs (n=671)
  - No improvement in histology

Drugs in Clinical Trials for NAFLD with Published Data

- Normal
- Steatosis
- Steatohepatitis
- Cirrhosis
- Metabolic
- Anti-inflammatory
- Anti-fibrotic

- Obeticholic Acid
- Elafibranor
- ACC Inhibitor
- GLP-1
- Aramchol
- NGM 286

- Emricasan
- Galactin 3 Inhibitor
- Cenicriviroc
- Selonsertib
### Actions of Obeticholic Acid (OCA)

- **FXR binding site**
- **Inflammation & fibrosis**
- **Lipid metabolism**
- **Carbohydrate metabolism**

- Exerts anti-inflammatory and anti-fibrotic effects in the liver, intestine, and kidney.
- Regulates insulin signaling and sensitivty, and hepatic gluconeogenesis.
- Deregulates hepatic fatty acid biosynthesis and VLDL formation.

---

### Therapeutic Trials for NAFLD

- **Obeticholic Acid**
  - RCT Phase II (n=283) “FLINT”
  - Improved steatosis, inflammation, and cellular injury, and fibrosis after 72 weeks.
  - Pruritis (23%), weight loss, increased LDL major AEs.

---

### Drugs in Clinical Trials for NAFLD with Published Data

- **Normal**
- Steatosis Metabolic
- Steatohepatitis Anti-inflammatory/ cell death
- Cirrhosis Anti-fibrotic

- **Obeticholic Acid**
- Elafibranor
- XCD Inhibitor
- GLP-1
- Aramchol
- NGM 286

- Emriscan
- Galactin 3 Inhibitor
- Cemivencos
- Selonsertib

---
Potential Therapeutic of Actions of Peroxisome Proliferator-activated Receptor α/δ agonist


Therapeutic Trials for NAFLD

- Elafibranor (PPARα/δ dual agonist)
  - RCT Phase II (n=276)
  - Improved inflammation and cellular injury only in those with NAS >4
  - No improvement in steatosis or fibrosis at 52 weeks
  - Mild increase in creatinine in 7.1%


Drugs in Clinical Trials for NAFLD with Published Data

- Obeticholic Acid
- Elafibranor
- GLP-1 Agonist
- Aramchol
- NGM 286

- Emricasan
- Galactin 3 Inhibitor
- Cenicriviroc
- Selonsertib

Normal

Steatosis

Metabolic

Steatohepatitis

Anti-inflammatory/ cell death

Cirrhosis

Anti-fibrotic
Therapeutic Potential of Acetyl-CoA Carboxylase (ACC) Inhibition

Browning and Horton, JCI. 2004.

ACC Inhibition in Humans Reduced Liver TGs by 44% in Subjects with NAFLD

MK-4074 Increased Plasma TGs ~2-fold

![Graph showing MK-4074 increased plasma TGs](image)


**Drugs in Clinical Trials for NAFLD with Published Data**

- **Normal**
  - Steatosis
  - Metabolic
  - Steatohepatitis
  - Anti-inflammatory/cell death
  - Cirrhosis
  - Anti-fibrotic

  - Obeticholic Acid
  - Elafibranor
  - ACC Inhibitor
  - GLP-1
  - Aramchol
  - NGM 286
  - Emricasan
  - Galactin 3 Inhibitor
  - Cenicriviroc
  - Selonsertib

**Case Presentation-? Therapy**

- 49 y/o Hispanic female presents for evaluation of abnormal LFTs found in health screen.
- Abdominal Sono: Increased echogenicity
- Dietary restriction for weight loss
- Bariatric surgery