State of the Art of Non-alcoholic Fatty Liver Disease: Where Are We And Where Are We Going?
25 January 2020
NAFLD Disclosures

• Clinical trials with Gilead, Genfit, Intercept, Galectin, Novo Nordisk, Allergan
• Speakers Bureau for Intercept
• Advisory Board for Gilead
Pre-Test Question 1

• The most common indication for liver transplant in the US in 2020 is
  a. Hepatitis C
  b. Hepatitis B
  c. Non-alcohol fatty liver disease
  d. Alcohol
Pre-Test Question 2

• Which of the following statements is true?
  a. Non-alcoholic fatty liver disease (NAFLD) is synonymous with non-alcoholic steatohepatitis (NASH)
  b. All patients with NASH have liver fibrosis (scarring) by definition
  c. Non-invasive blood and imaging tests can be used to estimate liver fibrosis (scarring) in patients with fatty liver disease
  d. All patients with NASH will develop cirrhosis
Pre-Test Question 3

• The likelihood that non-alcohol related fatty liver disease will progress to cirrhosis over 10 years is approximately
  a. 3%
  b. 20%
  c. 50%
  d. 80%
Pre-Test Question 4

• In an individual patient, NASH can most reliably be distinguished from alcohol-related steatohepatitis (ASH) on the basis of:
  a. Liver biopsy
  b. ALT value
  c. Alcohol history
  d. Ultrasound
Pre-Test Question 5

• Traditional cardiovascular risk models include which of the following parameters important to NASH
  a. Insulin resistance
  b. Hypertriglyceridemia
  c. Obesity
  d. None of the above
Non-alcoholic Fatty Liver Disease (NAFLD)

- Wide spectrum of liver disease with $\geq 5\%$ hepatic steatosis ranging from simple macrovesicular steatosis to steatohepatitis to cirrhosis
- 25% of Americans are affected
  - Hispanics > Caucasians > African Americans
- More common in males
- Accounts for up to $\frac{3}{4}$ cases of abnormal transaminases in the outpatient setting
- Most common cause of “cryptogenic” cirrhosis
Risk Factors for NAFLD

- Visceral obesity
- Hypertriglyceridemia
- Type 2 diabetes mellitus
  - Insulin resistance
- Medications
  - Tamoxifen, methotrexate, corticosteroids, amiodarone
- No apparent cause in 20-40%
  - This number will decrease when we have a better understanding of relevant genetic polymorphisms
Risk Factors for NAFLD

Prevalence\(^1\) of Self-Reported Obesity Among U.S. Adults by State and Territory, BRFSS, 2017

\(^1\)Prevalence estimates reflect BRFSS methodological changes started in 2011. These estimates should not be compared to prevalence estimates before 2011.
Conditions Associated with NAFLD

- Polycystic Ovarian Syndrome
- Pancreatico-duodenal resection
- Hypothyroidism
- Hypogonadism
- Obstructive sleep apnea
- Hypopituitarism
Familial Association with NAFLD

• 18% of patients with NASH have a similarly affected first degree relative (Willner Am J Gastroenterol 2001)

• Patients with NAFLD have a higher percentage of relatives with cirrhosis than matched controls (Abdelmalek 2006 Clin Gastroenterol Hep)

• Conclusive studies are lacking

• Systematic screening of relatives of patients with NAFLD is not recommended
Diagnosis of NAFLD

• Diagnosis of Exclusion
  – Absence of alcohol excess
    • Women ≤1-2 equivalents/d, men ≤ 2-3/d
  – AST and ALT < 10 times upper limit of normal
  – No specific serologic markers
    • Anti-smooth muscle and anti-nuclear antibodies may be weakly positive
  – Ferritin may be moderately elevated
Natural History of NAFLD

- **NAFLD***
  - Prevalence in US ~20%- 25%

- **NASH**
  - Prevalence ~3-5%

- **Cirrhosis**
  - Prevalence ~0.6-1%

- **ESLD**
  - Now #1 indication for liver transplant

- **HCC**
  - Lower incidence of hepatocellular carcinoma in NASH cirrhosis than in HCV cirrhosis

*NAFLD can spontaneously improve even without intervention*
Non-Alcoholic Steatohepatitis (NASH)

- Risk factors for progression of NAFLD→NASH are not clear
  - Highest rates in Hispanics and in DM
  - Metabolic syndrome predicts the presence of NASH
  - Possible role of polymorphisms, such as the patatin-like phospholipase-domain-containing protein 3 (PNPLA-3) gene
- ALT poor at differentiating NAFLD from NASH
- Role for non-invasive ancillary biomarkers
Distinguishing NAFLD vs. NASH

• Liver Biopsy
  – For patients at increased risk of NASH and advanced fibrosis or in whom competing etiologies for steatosis and chronic liver disease haven’t been excluded
  – Hepatic steatosis and inflammation with hepatocyte ballooning +/- fibrosis
• Prognostic Implications of Histology
  – Steatosis → 3-4% cirrhosis in > 10yr
  – NASH → 20-30% cirrhosis in 10 yr
Assessing Liver Fibrosis in NAFLD

- **Liver biopsy**
  - Gold standard
  - Samples 1/50,000 liver
  - Grades inflammation and stages fibrosis
  - Risks
    - Bleeding, infection, injuring nearby organs
    - May be minimized by using transjugular route
  - Biopsy is not 100% sensitive or specific

- **Non-invasive ancillary biomarkers**
  - Fib-4
    - Age x AST/platelet x √ALT
  - NAFLD fibrosis score
    - Age, BMI, hyperglycemia, platelet count, albumin, and AST/ALT ratio
  - Transient elastography
    - Failure rate lower with an XL probe
  - MR elastography with proton density fat fraction
    - Lower failure rate with ↑ BMI
Vibration Controlled Transient Elastography with Controlled Attenuation Parameter

Advanced Fibrosis Due to NASH Represents a Subset of the NASH Population

Estes et al Hepatology 2018
Some Patients with Advanced Fibrosis Due to NASH Will Progress to Cirrhosis Quickly

Rapid progression of patients with F3 to cirrhosis

After approximately 2.5 years, 1 in 5 progressed to cirrhosis

*Sanyal et al. Hepatology 2019
NASH and Hepatocellular Carcinoma (HCC)

• HCC is the 3rd leading cause of cancer deaths worldwide
• HCC is the fastest growing cause of cancer deaths in the US (El Serag Gastroenterology 2007, Seef Gastroenterology 2004)
• The annual incidence of HCC associated with HCV is still higher than with NASH (4.0 vs. 2.6%)
  – From 2002-2012, the increase in incidence of HCC was higher for NASH with BMI > 25 kg/m² than for HCV (364% vs. 225%) (Wong Hepatology 2014)
HCC in NASH is Not Restricted to Cirrhosis

• 41-56% NASH-related HCC occurs in the absence of cirrhosis (Mittal Clin Gastroenterol and Hepatol 2014, Yasui Clin Gastroenterol and Hepatol 2011)
• Older males with metabolic syndrome are at greatest risk (Hashimoto J of Gastroenterol 2009)
• Tumor biology might be different
  – Lower alpha fetoprotein and higher des-g-carboxy prothrombin
• Patients with NAFLD-related HCC have a shorter survival time, more often have heart disease, and are more likely to die from their primary liver cancer than other patients with HCC (Mohamad et al Hepatol Int 2016)
• HCC screening recommendations for NAFLD without cirrhosis are unclear
Mortality of NAFLD

• Individuals with NAFLD have higher mortality than those without NAFLD (Adams Gastroenterol 2005)
  – Increase in mortality is in the subset of pts with NASH (Ekstedt Hepatology 2006, Kim Hepatology 2013)

• Cause of death
  – Malignancy 27%
  – Ischemic Heart Disease 25%
  – Liver Disease 13%
## Association between Fibrosis and Overall and Cause-Specific Mortality Among Subjects with NAFLD

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Multi-variable adjusted Hazard Ratio (95% CI) for Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All cause</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimal Fibrosis</td>
<td>251</td>
<td>1</td>
</tr>
<tr>
<td>Intermediate Fibrosis</td>
<td>404</td>
<td>1.40 (1.09-1.81)</td>
</tr>
<tr>
<td>Advanced Fibrosis</td>
<td>123</td>
<td>1.80 (1.23-2.64)</td>
</tr>
<tr>
<td><strong>Cardiovascular disease</strong></td>
<td>296</td>
<td></td>
</tr>
<tr>
<td>Minimal Fibrosis</td>
<td>81</td>
<td>1</td>
</tr>
<tr>
<td>Intermediate Fibrosis</td>
<td>167</td>
<td>2.49 (1.71-3.64)</td>
</tr>
<tr>
<td>Advanced Fibrosis</td>
<td>48</td>
<td>3.22 (1.92-5.42)</td>
</tr>
</tbody>
</table>

Kim Hepatology 2013
Treatment of NASH

• Diet and exercise
  – Best evidence from a trial that randomized 31 obese persons with NASH to intensive lifestyle changes (diet, behavior modification, moderate physical activity) vs. education alone (Promrat Hepatology 2010)
    • Intensive arm had 9.3% weight loss vs. 0.2% (p 0.003)
    • 72% in lifestyle arm vs. 30% in control (p =0.03) had improvement in steatosis, necrosis and inflammation, but not fibrosis
    • Participants with ≥7% weight loss had significant improvement in steatosis, lobular inflammation, ballooning and NALFD activity score
Degree of Weight Loss and Resolution of NAFLD*

Weight Loss and Resolution of NAFLD by MR spectroscopy

% Pts with Resolution of NAFLD

% Weight Loss

< 3.0% 3-4.9% 5.0-6.9% 7.0-9.9% >= 10.0%

*Wong VW Hepatology 2013
Pioglitazone, Vitamin E or Placebo for NASH

• 247 non-diabetic pts with NASH randomized to pioglitazone (30 mg/d), vitamin E 800 (IU/d) or PBO for 24 months

• Primary endpoint was an improvement in NAFLD activity score by 2 points and no increase in fibrosis score
  – 43% vitamin E vs. 34% pioglitazone vs. 19% placebo

• In other trials, concerns raised with these drugs
  – congestive heart failure with pioglitazone
  – all cause mortality and prostate CA with vitamin E

Sanyal NEJM 2010
Bariatric Surgery for NAFLD/NASH*

• Mathurin *et al* (Gastroenterology 2009) correlated clinical and metabolic data with liver histology before, 1 and 5 years after surgery in 381 pts
  – Gastric band 56%, bilio-intestinal bypass 23%, gastric bypass 21%
• Significant improvement in prevalence and severity of steatosis and ballooning
• In the 99 pts with baseline NASH, there was also improvement in NAFLD activity score and resolution of probable or definite NASH

*Liver disease not considered an indication for bariatric surgery per insurers*
Therapeutic targets for NASH (courtesy of Neuschwander-Tetri)

**Energy Intake and Disposal**
- Fructose + Glucose → Acetyl CoA
- De novo lipogenesis ("DNL")
- Circulating free fatty acids
- Chylomicron triglycerides
- Muscle, Brown adipose tissue (BAT)

**Liver**
- Free fatty acids
- Triglyceride
- MOGAT2, DGAT2
- Carnitine CPT1, CPT2
- PNPLA3?
- OCA

**Response to Injury**
- Hepatocellular injury
- Inflammation
- Lipotoxic lipids
- SREBP-1c
- ACC, FAS, SCDs
- Adipose tissue IR
- Adipose tissue
- Choline/PC, Acetyl CoA, ACC, FAS, SCDs

**Hepatic fatty acid metabolism**
- Hypertriglyceridemia
- VLDL
- Amino acids, Choline/PC
- Steatosis
- Mitochondrial beta-oxidation

**“NASH”**
- Fibrosis
- HCC
Potential New Targets for NASH in Clinical Development

- Steroidal and non-steroidal nuclear receptor farnesoid-X receptor agonists
- Peroxisome proliferator-activated receptor (PPAR) α/δ agonists
- CCR2/5 inhibitors
- Apoptosis signal-regulating kinase-1 inhibitors
- Acetyl-CoA carboxylase inhibitors
- Glucagon-like peptide-1 agonists
- Thyroid hormone receptor β-selective agonists
- Lysyl oxidase-like 2 inhibitors
- Stearoyl-CoA desaturase 1 inhibitors
- Galectin inhibitors
- Gut microbiome
- Bile acids are the major natural ligands of the FXR nuclear receptor
- FXR is the sensor for increased bile acids → decreased synthesis, increased export
Phase 2 FLINT trial

- Obeticholic acid, 25 mg orally daily vs placebo
- Inclusion: adults with NASH on biopsy, NAFLD Activity Score ≥ 4
- Exclusion: cirrhosis
- N = 283 patients randomized at 8 clinical centers
- 72 weeks of treatment
- Biopsy ≤ 3 mo. before treatment and after 72 weeks
- Primary endpoint
  - Improvement in NAFLD activity score ≥ 2 pts with no worsening of fibrosis

Flint trial results

Serum lipids in FLINT trial

Adverse events in the FLINT trial

- 6 severe adverse events in obeticholic acid group
  - 4 severe pruritus (1 stopped treatment)
  - 1 hypoglycemia
  - 1 possible cerebral ischemia (dysarthria and dizziness)

- Pruritus
  - 23% in obeticholic acid
  - 6% in placebo

\[ P < 0.0001 \]
Liver Transplant for NASH

• Substantial increase in the proportion of patients undergoing transplant in the US with a primary diagnosis of NASH from 1.2% in 2001 to 9.7% in 2009 (Charlton Gastroenterol 2011)

• Patient and graft survivals are similar to that for other major indications over 3-5 years
  – Longer follow up is needed since NASH shares risk factors for cardiovascular and chronic kidney disease

• NASH recurs after transplant (Yalamanchilli Liver Transpl 2010)
  – 60% steatosis, 10-40% NASH
  – About 10% with cirrhosis 10 yr after LT
Cardiovascular Events within 1 Year of Liver Transplant

Odds ratio for any CV event 2.69 (95% CI: 1.32-6.34)

Van Wagner Hepatology 2012
Pre-Test Question 1

• The most common indication for liver transplant in the US in 2020 is
  a. Hepatitis C
  b. Hepatitis B
  c. Non-alcohol fatty liver disease
  d. Alcohol
Pre-Test Question 2

• Which of the following statements is true?
  a. Non-alcoholic fatty liver disease (NAFLD) is synonymous with non-alcoholic steatohepatitis (NASH)
  b. All patients with NASH have liver fibrosis (scarring) by definition
  c. Non-invasive blood and imaging tests can be used to estimate liver fibrosis (scarring) in patients with fatty liver disease
  d. All patients with NASH will develop cirrhosis
Pre-Test Question 3

- The likelihood that non-alcohol related fatty liver disease will progress to cirrhosis over 10 years is approximately
  a. 3%
  b. 20%
  c. 50%
  d. 80%
In an individual patient, NASH can most reliably be distinguished from alcohol-related steatohepatitis (ASH) on the basis of:

a. Liver biopsy
b. ALT value
c. Alcohol history
d. Ultrasound
Pre-Test Question 5

• Traditional cardiovascular risk models include which of the following parameters important to NASH
  a. Insulin resistance
  b. Hypertriglyceridemia
  c. Obesity
  d. None of the above
Thank You
# NAFLD Nomenclature

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-alcoholic fatty liver disease (NAFLD)</td>
<td>Presence of ≥ 5% hepatic steatosis without evidence of hepatocellular injury in the form of hepatocyte ballooning or evidence of fibrosis. The risk of progression to cirrhosis and liver failure is minimal</td>
</tr>
<tr>
<td>Non-alcoholic steatohepatitis (NASH)</td>
<td>Presence of ≥ 5% hepatic steatosis with inflammation and hepatocyte ballooning with or without fibrosis. This can progress to cirrhosis, liver failure, and rarely liver cancer. Note: NASH can be present without fibrosis.</td>
</tr>
<tr>
<td>NASH cirrhosis</td>
<td>Presence of cirrhosis with current or previous histological evidence of steatosis or steatohepatitis</td>
</tr>
<tr>
<td>NAFD activity score (NAS)</td>
<td>An unweighted composite of steatosis, lobular inflammation, and ballooning scores on liver biopsy. NAS is used to measure changes in histology in clinical trials. Fibrosis is scored separately from NAS</td>
</tr>
</tbody>
</table>

From Chalasani et al Hepatology 2018;67:328-357
Non-Invasive Serum Ancillary Biomarkers for Distinguishing NAFLD from NASH

• FIB-4
• NAFLD fibrosis score (NFS)
  – Age, BMI, hyperglycemia, platelet count, albumin, and AST/ALT ratio
  – AUROC 0.85 for predicting advanced fibrosis
• NFS and FIB-4 are as good as MRE for predicting fibrosis in patients with biopsy-proven NAFLD (Imajo et al Gastroenterology 2016)
• Enhanced liver fibrosis (ELF) score
  – 3 matrix turnover proteins(hyaluronic acid, tissue inhibitor of metalloproteinase 1, and N-terminal procollagen III-peptide)
  – AUROC of 0.90 for detecting advanced fibrosis (Angulo et al Hepatology 2007)
Despite limitations, liver biopsy results have been shown to be effective at predicting patient outcomes*\(^1\)

<table>
<thead>
<tr>
<th>Fibrosis stage</th>
<th>Kaplan-Meier survival estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td>F0</td>
<td>Controls</td>
</tr>
<tr>
<td>F1</td>
<td>F2</td>
</tr>
<tr>
<td>F2</td>
<td>F3</td>
</tr>
<tr>
<td>F4</td>
<td></td>
</tr>
</tbody>
</table>

Fibrosis stage determined by liver biopsy predicts risk of all-cause mortality in NAFLD patients\(^1\)

*From a retrospective cohort study of 646 biopsy-proven NAFLD patients, each matched to 10 controls

Adapted from Hagström H et al. *J Hepatol* 2017;67:1265–1273

NAFLD, nonalcoholic fatty liver disease
Sleeve Gastrectomy

- Increased satiety
  - Stretch mechanoreceptor activation
  - Removal of ghrelin producing fundus
  - Decreased appetite
  - Increased FXR signaling
Current Indications for Bariatric Surgery

- BMI
  - > 40 kg/m²
  - > 35 kg/m²
    - with diabetes mellitus, obstructive sleep apnea, hypertension, heart failure
    - **Liver disease not included**
- Multiple failed weight loss attempts
- Acceptable surgical risk
  - No significant portal hypertension
- 18-60 years old