NAFLD and NASH

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Disclosures

- Consultant
  - Gilead
- Speakers’ Bureau
  - Gilead
# The Global Prevalence of NAFLD

<table>
<thead>
<tr>
<th>Region</th>
<th>N</th>
<th>Prevalence (%)</th>
<th>95% CI (%)</th>
<th>I² (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>2</td>
<td>13.48</td>
<td>(5.69 - 28.69)</td>
<td>84.37</td>
</tr>
<tr>
<td>Asia</td>
<td>14</td>
<td>27.37</td>
<td>(23.29 - 31.88)</td>
<td>99.17</td>
</tr>
<tr>
<td>Europe</td>
<td>11</td>
<td>23.71</td>
<td>(16.12 - 33.45)</td>
<td>98.78</td>
</tr>
<tr>
<td>Middle East</td>
<td>3</td>
<td>31.79</td>
<td>(13.48 - 58.23)</td>
<td>99.14</td>
</tr>
<tr>
<td>North America</td>
<td>13</td>
<td>24.13</td>
<td>(19.73 -29.15)</td>
<td>99.19</td>
</tr>
<tr>
<td>South America</td>
<td>2</td>
<td>30.45</td>
<td>(22.74 - 39.44)</td>
<td>69.10</td>
</tr>
<tr>
<td>Overall</td>
<td>45</td>
<td>25.24</td>
<td>(22.1 - 28.65)</td>
<td>99.07</td>
</tr>
</tbody>
</table>

Younossi Z et al. Hepatology 2015
NAFLD: Most common cause of CLD and Cirrhosis

NAFLD Disease Progression

Histological Subtypes\(^1,2\)

- Isolated steatosis
- Steatosis with mild inflammation
- NASH
- Cirrhosis
- Fibrosis

Change in Fibrosis\(^3,4\)

- Regression: 18%-22%
- Stable: 40%-43%
- Progression: 34-42%

*\(N = 108\) pts with NAFL/NASH and median 6.6 yrs follow-up (data from serial biopsies).

Mortality in Patients With NAFLD

- Patients with NAFLD (N = 420) matched by age and sex to general population in Minnesota, followed for 7.6 ± 4.0 yrs

Top 3 Causes of Death in NAFLD, %

<table>
<thead>
<tr>
<th>Cause</th>
<th>Patients (n = 53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignancy</td>
<td>28</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>25</td>
</tr>
<tr>
<td>Liver disease</td>
<td>13</td>
</tr>
</tbody>
</table>

Survival at 10 Yrs

- General population: 87%
- Patients with NAFLD: 77%
- Log-rank $P < .005$

Mortality Due to NASH Among Patients With NAFLD

- Patients with NAFLD (N = 129) matched by age and sex within same county in Sweden and followed for 13.7 yrs (SD: 1.3 yrs)

NAFLD & HCC

Dyson J et al; Hep 2014
Association Between NAFLD/NASH and Diabetes Mellitus Is Bidirectional

Patients with NAFLD/NASH have:

- Increased risk of developing diabetes\textsuperscript{[1,2]}
- Synergistic increase in risk of diabetes when combined with obesity or insulin resistance\textsuperscript{[3]}
  - Patients with obesity, NAFLD, or insulin resistance each have 2-4 x the risk of diabetes, but patients with all 3 have 14 x risk of diabetes
- High prevalence of diabetes\textsuperscript{[4]}

Patients with diabetes have:

- Increased risk of NASH with family history of diabetes\textsuperscript{[5]}
- Increased risk of dying from cirrhosis\textsuperscript{[6,7]}
- Up to 3-fold increased risk of dying from chronic liver disease, mostly attributable to NAFLD\textsuperscript{[8]}
- Increased risk of chronic liver disease\textsuperscript{[9]}

References in slidenotes.
Clinical Predictors of NASH in Patients With NAFLD

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced age</td>
<td>Greater duration of disease</td>
</tr>
<tr>
<td>Sex</td>
<td>Postmenopausal women experience accelerated disease</td>
</tr>
<tr>
<td>Race</td>
<td>↑ Prevalence, severity in Hispanic, Asian patients; ↓ Prevalence, severity in black patients</td>
</tr>
<tr>
<td>HTN, central obesity, dyslipidemia (↑ TG, ↓ HDL), insulin resistance/diabetes</td>
<td>Risk increases with metabolic syndrome,* 66% prevalence of bridging fibrosis if older than 50 yrs of age and obese or diabetic[^5,6^]</td>
</tr>
<tr>
<td>AST/ALT ratio &gt; 1, low platelets</td>
<td>Indicators of NASH cirrhosis</td>
</tr>
<tr>
<td>Persistently elevated ALT</td>
<td>Can be associated with greater risk of disease progression</td>
</tr>
</tbody>
</table>

*Based on ATP III criteria.
Normal ALT Does Not Rule Out Progressive Disease in NAFLD or NASH

- Persistently elevated ALT can be associated with disease progression[1]

- Patients with normal ALT levels can also develop progressive disease[2-4]
  - Up to 80% of NAFLD patients can have normal ALT[5]

- No designated ALT cutoff for prediction of NASH or advanced fibrosis in NAFLD pts[6]

# Noninvasive Diagnosis of Liver Fibrosis in NAFLD

## Clinical or Laboratory Tests

**Simple**
- AST/platelet ratio index
- FIB-4 index
- NAFLD fibrosis score
- BARD score

**Complex**
- NASH *FibroSure*
- ELF
- HepaScore

## Imaging

**Elastography**
- VCTE *FibroScan*
- MR elastography
- ARFI
# NAFLD Fibrosis Score

## NAFLD Fibrosis Score:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td></td>
</tr>
<tr>
<td>AST</td>
<td></td>
</tr>
<tr>
<td>ALT</td>
<td></td>
</tr>
<tr>
<td>Platelet count, cells x 10⁹</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td></td>
</tr>
<tr>
<td>Albumin, g/L</td>
<td></td>
</tr>
<tr>
<td>Impaired fasting glucose/diabetes?</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NAFLD Cutoff Value[1]</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; -1.455</td>
<td>F0-F2</td>
</tr>
<tr>
<td>-1.455 to 0.676</td>
<td>Indeterminate</td>
</tr>
<tr>
<td>&gt; 0.676</td>
<td>F3-F4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FIB-4 Cutoff Value[2]</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1.45</td>
<td>F0-F2</td>
</tr>
<tr>
<td>1.45 to 3.25</td>
<td>Indeterminate</td>
</tr>
<tr>
<td>&gt; 3.25</td>
<td>F3-F4</td>
</tr>
</tbody>
</table>

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# Tools for Diagnosis of NAFLD

<table>
<thead>
<tr>
<th>Method</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver enzymes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ GGT[1]</td>
<td>63%</td>
<td>65%</td>
<td>Not reliable for diagnosis</td>
</tr>
<tr>
<td>Ultrasound[2]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Any degree[3]</td>
<td>85%</td>
<td>94%</td>
<td>Inexpensive and accessible, but cannot distinguish fibrosis/steatosis</td>
</tr>
<tr>
<td>▪ Cutoff ≥ 20%[3]</td>
<td>61%</td>
<td>100%</td>
<td>Better in morbid obesity, but affected by iron, fibrosis, and less accurate with less steatosis</td>
</tr>
<tr>
<td>CT without contrast[4]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Cutoff &gt; 30%</td>
<td>79%</td>
<td>97%</td>
<td></td>
</tr>
<tr>
<td>MRI[5]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Cutoff PDFF 6.4%, gr ≥ 1</td>
<td>86%</td>
<td>83%</td>
<td>Detects mild steatosis, quantifies hepatic fat most accurately</td>
</tr>
<tr>
<td>▪ Cutoff PDFF 17.4%, gr ≥ 2</td>
<td>64%</td>
<td>96%</td>
<td></td>
</tr>
<tr>
<td>MRS[6]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Cutoff ≥ 5%</td>
<td>90-96%</td>
<td>87-100%</td>
<td></td>
</tr>
<tr>
<td>▪ Cutoff &gt; 33%</td>
<td>92-100%</td>
<td>92-97%</td>
<td></td>
</tr>
<tr>
<td>Liver biopsy</td>
<td></td>
<td></td>
<td>Gold standard, but invasive and subject to sampling error</td>
</tr>
</tbody>
</table>

References in slidenotes.
## Diagnostic Performance of Supersonic Shear Imaging, *FibroScan*, and ARFI

<table>
<thead>
<tr>
<th>Fibrosis Stage</th>
<th>AUROC (95% CI)</th>
<th>Best Accuracy, % (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Supersonic shear imaging</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ F2</td>
<td>0.86 (0.79-0.90)</td>
<td>80 (185/232)</td>
</tr>
<tr>
<td>≥ F3</td>
<td>0.89 (0.83-0.92)</td>
<td>85 (196/232)</td>
</tr>
<tr>
<td>F4</td>
<td>0.88 (0.82-0.92)</td>
<td>87 (202/232)</td>
</tr>
<tr>
<td><strong>FibroScan</strong> (M probe only)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ F2</td>
<td>0.82 (0.76-0.87)</td>
<td>77 (172/223)</td>
</tr>
<tr>
<td>≥ F3</td>
<td>0.86 (0.80-0.90)</td>
<td>79 (175/223)</td>
</tr>
<tr>
<td>F4</td>
<td>0.87 (0.79-0.92)</td>
<td>89 (198/223)</td>
</tr>
<tr>
<td><strong>ARFI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ F2</td>
<td>0.77 (0.70-0.83)</td>
<td>74 (175/236)</td>
</tr>
<tr>
<td>≥ F3</td>
<td>0.84 (0.78-0.89)</td>
<td>79 (186/236)</td>
</tr>
<tr>
<td>F4</td>
<td>0.84 (0.78-0.89)</td>
<td>84 (199/236)</td>
</tr>
</tbody>
</table>

Can Noninvasive Clinical or Lab Tests Distinguish NASH Stages 0-2 vs 3-4?

- Strength of noninvasive fibrosis predictive tests is in their ability to exclude advanced disease (F3-F4)
  - Least accurate in identifying middle ranges of fibrosis

Magnetic Resonance Elastography

- In NAFLD, higher diagnostic accuracy for fibrosis vs transient elastography and CPRs,\[^2,3\] can accurately predict advanced fibrosis\[^4\].
- Inflammation can increase stiffness values in the absence of fibrosis\[^1\].

Reprinted, with permission, from Radiology 2011;259:749-756. ©RSNA. References in slidenotes.
The Role of Liver Biopsy

- **Make diagnosis of NASH** (surrogates insufficient)[1]
  - Initiate drug therapy
  - Assess prognosis: liver, cardiovascular, etc
- **Stage fibrosis** (if imaging or tests are indeterminate)[1]
- **Rule out concomitant liver disease**[1]
  - Autoimmune, Wilson disease, DILI, iron overload (ferritin can be high in NAFLD in absence of iron overload[2])

Fibrosis Staging in NASH

F1: Perisinusoidal

F2: Perisinusoidal + Portal

F3: Bridging Fibrosis

F4: Cirrhosis
Prognostic Relevance of Liver Histology in Nonalcoholic Fatty Liver Disease: The PRELHIN study

- International study of NAFLD (N=619) diagnosed between 1975-2005
- All liver biopsies centrally ready
- Median follow-up 12.6 yrs
- 193 who died or had OLT
  - 74 (38.3%) of CV disease
  - 36 (18.7%) of non-liver CA

### Multivariate Analysis

<table>
<thead>
<tr>
<th>Fibrosis Stage</th>
<th>Hazard Ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (ref)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2.4 (0.63, 8.91)</td>
<td>0.2</td>
</tr>
<tr>
<td>2</td>
<td>7.5 (2.26, 24.94)</td>
<td>0.01</td>
</tr>
<tr>
<td>3</td>
<td>13.8 (4.35, 43.65)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>4</td>
<td>47.5 (11.94, 188.61)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Because “Histologic NASH” and “stage of fibrosis” are predictors of mortality, they have become important study endpoints.
Management Strategies

- Identification of the risk of NASH and disease progression is guided by:
  - Clinical risk factors (eg, metabolic, family history)
  - Noninvasive markers
    - Fairly accurate to diagnose advanced fibrosis
      - Know the confounders
    - Lesser cutoffs on imaging in combination with other factors can predict NASH with modest accuracy
    - Can reliably exclude advanced fibrosis but not NASH
Risk Stratification in Pts With Suspected NAFLD

Low-risk profile
- BMI < 29.9
- Age < 40 yrs
- No T2DM or metabolic syndrome features
- Noninvasive fibrosis estimation:
  - FIB-4 < 1.30
  - APRI < 0.5
  - NFS < -1.455
- FibroScan < 5 kPa

Intermediate-risk profile
- BMI > 29.9
- Age > 40 yrs
- Multiple features of the metabolic syndrome
- Noninvasive fibrosis estimation:
  - FIB-4 1.30-2.67
  - APRI 0.5-1.5
  - NFS -1.455-0.675
- FibroScan 6-11 kPa

High-risk profile
- AST level > AST level
- Platelets < 150,000
- Noninvasive fibrosis estimation:
  - FIB-4 > 2.67
  - APRI > 1.5
  - NFS > 0.675
- FibroScan > 11 kPa

Follow and reassess as risk factors evolve

Evaluate alcohol consumption

Confirm NAFLD

Exclude alternate causes of ↑ALT levels

Hepatic steatosis on imaging ± elevated serum ALT levels

Consider liver biopsy

Consider liver biopsy or confirmatory testing for cirrhosis (eg, MRE)

Percentage of Weight Loss Associated With Histological Improvement in NAFLD

- Analysis of data from 4 randomized studies

  Weight loss ≥ 10%
  - Fibrosis regression (45% of pts)

  Weight loss ≥ 7%
  - NASH resolution (64% to 90% of pts)*

  Weight loss ≥ 5%
  - Ballooning/inflammation (41% to 100% of pts)*

  Weight loss ≥ 3%
  - Steatosis (35% to 100% of pts)*

* Depending on degree of weight loss.

PIVENS: Histologic Resolution of NASH at Wk 96 With Vitamin E vs Pioglitazone

- Double-blind, placebo-controlled, randomized, phase III trial in adults with biopsy-proven NASH and no diabetes or cirrhosis (N = 247)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Pts With Resolved NASH (%)</th>
<th>n/N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin E</td>
<td>36</td>
<td>29/80</td>
</tr>
<tr>
<td>Placebo</td>
<td>21</td>
<td>15/72</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>47</td>
<td>33/70</td>
</tr>
</tbody>
</table>

Pioglitazone in Diabetes: Improvement or Resolution of NASH at 18 Mos

- Randomized, placebo-controlled, double-blind phase IV trial of pts with NASH and prediabetes or type 2 diabetes mellitus (N = 101)[1]
  - Secondary outcome analysis of histologic scores included pts with paired biopsies from before/after tx (n = 82)

# Pharmacologic Treatment Options Studied in NASH

<table>
<thead>
<tr>
<th>Agent</th>
<th>Good Evidence for Use(^1)</th>
<th>Limited or Insufficient Evidence for Use(^1)</th>
<th>AASLD NAFLD/NASH Recommendation(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin E</td>
<td>NASH without diabetes</td>
<td>NASH with diabetes or cirrhosis</td>
<td>NASH without diabetes</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>NASH with or without diabetes</td>
<td>NASH with cirrhosis</td>
<td>Can be used for steatohepatitis</td>
</tr>
<tr>
<td>Metformin</td>
<td>No significant effect on liver histology(^2)</td>
<td></td>
<td>Not recommended</td>
</tr>
<tr>
<td>Pentoxifylline</td>
<td>Needs further study to determine ideal subpopulation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Bariatric Surgery Improves Fibrosis in Pts With NASH

- Prospective study of bariatric surgery in pts who are morbidly obese with biopsy-validated NASH, ≥ 1 comorbidity factor for > 5 yrs, no chronic liver disease (N = 109)

Distribution of Fibrosis METAVIR Scores

Baseline vs After 1 Yr

<table>
<thead>
<tr>
<th>Fibrosis METAVIR Score</th>
<th>Pts (%)</th>
<th>Wilcoxon signed-rank paired t test</th>
</tr>
</thead>
<tbody>
<tr>
<td>F4</td>
<td>21.25</td>
<td>-3.75 -7.5 P &lt; .003</td>
</tr>
<tr>
<td>F3</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>F2</td>
<td>27.5</td>
<td></td>
</tr>
<tr>
<td>F1</td>
<td>43.75</td>
<td></td>
</tr>
<tr>
<td>F0</td>
<td>13.75</td>
<td></td>
</tr>
</tbody>
</table>

FXR Central to a Multitude of Key Pathways in Animal Models

- ↓ Portal pressure
- ↓ Inflammation
- ↓ Fibrosis
- ↓ stellate cell activation
- via ↑ iNOS
- via ↓ SREPB-1C
- via ↑ β-oxidation

- ↑ Cholesterol
- ↑ Bile acids
- ↓ Hepatic triglycerides
- ↓ Glucose tolerance

Multiple mechanisms via ↓ SREPB-1C through RXR

FXR agonist (eg, obeticholic acid)

References in slidenotes.
## Emerging Treatments in NASH: Phase III

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Study Population</th>
<th>Trial</th>
<th>Primary Endpoint(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obeticholic acid</td>
<td>FXR agonist (bile acid)[3]</td>
<td>NASH with fibrosis</td>
<td>REGENERATE[4,5]</td>
<td>Improvement in fibrosis w/o NASH worsening; improvement in NASH w/o fibrosis worsening</td>
</tr>
</tbody>
</table>

2. ClinicalTrials.gov. NCT02704403.
Obeticholic Acid: FXR Agonist and Bile Acid Analogue

CDCA (chenodeoxycholic acid)

OCA (6-ECDDCA) (obeticholic acid)

~ 90 x increased potency

FXR EC<sub>50</sub> = 8.7 µM

FXR EC<sub>50</sub> = 99 nM

- In vitro/in vivo studies do not necessarily correlate with clinical response

**Dual PPARα/δ Agonist**

**Elafibranor**

PPARα:
- Fatty acid oxidation
- TG lowering
- HDL raising
- Inflammation

PPARδ:
- Lipoprotein metabolism
- Glucose homeostasis
- Energy metabolism
- Inflammation

Liver

Slide courtesy of Bart Staels, MD.
Key NASH Therapies: Improvement in Steatosis

- Results from separate studies, not head to head
  - Time points and populations may differ between studies

- In bariatric surgery study, median steatosis improved from 60% at baseline to 10% at 1 yr

References in slides notes.
Key NASH Therapies: Resolution of NASH

- Results from separate studies, not head to head
  - Time points and populations may differ between studies

References in slidenotes.
Key NASH Therapies: Improvement in Fibrosis

- Results from separate studies, not head to head
  - Time points and populations may differ between studies

References in slidenotes.
Summary

- Lifestyle changes are the foundation of any treatment plan
  - Weight loss ≥ 3% to 10% associated with histologic improvement in NAFLD

- AASLD guidance cites evidence for vitamin E (NASH without diabetes), pioglitazone (NASH with or without diabetes), bariatric surgery

- Preliminary evidence for improvement in fibrosis with some investigational therapies